Classical Swine Fever

Disease Monograph Series – 07

Virus | Flaviviridae | *Pestivirus* | Pigs

IDRC | Bartay

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Acronyms

ASEAN	Association of South East Asian Nations
C	Chinese ‘C’ strain
DIVA	Differentiating infected from vaccinated animals
dpi	Days post infection
E	Envelope proteins (E, E1, and E2)
E^{rns}	E0 glycoprotein
ELISA	Enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
FAT	Fluorescent antibody test
FAVN	Fluorescent antibody virus neutralization test
GPE–	Japanese guinea-pig exaltation-negative strain
N^{pro}	N-terminal autoprotease
NPLA	Neutralising peroxidase-linked assay
NS	Nonstructural protein
NTR	Non-translated region
OIE	World Organization for Animal Health
p7	Virus ionic channel protein
PK	Porcine kidney cell culture

PAV	Live attenuated Mexican strain
PRRS	Porcine Respiratory and Reproduction Syndrome virus
PRV	Pseudorabies virus (Aujesky's disease)
RT-PCR	Reverse transcription polymerase chain reaction
SAARC	South Asia Association for Regional Cooperation
TADs	Transboundary animal diseases
USA	United States of America
VI	Virus isolation
WAHID	Interface for the World Animal Health Information System
WAHIS	World Animal Health Information System Database

Executive Summary

Classical swine fever virus (CSFV) is a small, enveloped RNA virus in the genus *Pestivirus* of the family Flaviviridae. CSFV is related to the other pestiviruses, including bovine viral diarrhea virus of cattle and border disease virus of sheep [1][2]. Congenital infections with ruminant pestiviruses in pigs occasionally give rise to a clinical disease that is indistinguishable from classical swine fever (CSF) [2]. The genome of CSFV includes 12 proteins including the capsid protein C and three envelope proteins (E^{rns}, E1, and E2). Both E^{rns} and E2 are known to induce viral neutralizing antibodies, which give protective immunity in the pigs [5]. All CSFV react as a single serotype and are classified into three major genotypes and ten subtypes (sub-genotypes) [4]. Most of the highly virulent CSFV strains belong to genotype 1 which also includes the vaccine strains. Moderately virulent strains belong to genotypes 2 and 3.

The CSF viruses affect domesticated pigs and wild boars with variable symptoms according to the virus strain, exposure history and host genetics [2][3]. The clinical signs of CSFV are not pathognomonic and include an acute form, a chronic form and a congenital form. The incubation period of CSFV in pigs is 2-14 days [1][4]. The virus replicates in the tonsils and regional lymph nodes, after which viral shedding from faeces and urine begins 6-9 days post-infection [10]. Both direct and indirect transmission can follow. Direct transmission can be from horizontal and vertical transmission. Indirect transmission can also occur via humans, transported vehicles, artificial insemination, pork and pork products and fomites [14][10]. Congenitally infected piglets and chronically infected adult pigs act as long term silent carriers of CSFV with suppressed antibody production in chronically infected piglets. The European wild boar acts as a non-classical reservoir for CSFV. Information about the role of wild and feral pigs in Asia is lacking.

CSFV is the highest impact pig disease accounting for the greatest global pig losses measured in livestock units lost [37]. There were a total of 4,938 CSFV events reported by the 20 selected countries under the Livestock Vaccine Innovation Fund (LVIF) between 2000 and 2015. Forty-eight per cent (48%) of all CSFV events were reported in Viet Nam while 42% were reported in India. Nepal (5%), Madagascar (2%), South Africa (2%) and Myanmar (1%) accounted for the remainder of the reported events. The method of choice for detecting herds early in infection is to collect whole blood and tissues from febrile or recently dead animals. Recommended tissues to collect include tonsil, lymph nodes (pharyngeal, mesenteric), spleen, kidney, distal ileum, blood in EDTA or in Heparin tubes (live cases). The virus can survive in the environment, for three days at 50°C and 7-15 days at 37°C. It can survive for years at -70°C. Rapid temperature changes are harmful. The CSFV can survive for 90 days in frozen meat and 188 days in ham [11].

CSFV is reported in Europe, Central and South America, the Caribbean and Asia either through epidemics of particular strains or as an endemically established disease, which results in high mortality in pigs and wild boars [7][8]. The main risks for transmission of CSFV include the movement of pigs that are incubating the disease or are persistently infected; indirect spread of virus through transport vehicles; human contacts; and feeding uncooked pork wastes.

Culling remains the most effective way to control CSFV. However, this method is not sustainable or acceptable for developing countries. Vaccination remains the preferred tool for prevention and control for smallholder pig production units. The most common vaccine strain used globally is the Chinese 'C' strain. The GPE– strain, the Thiverval strain, and the Mexican PAV strains are regionally applied [47]. The subunit marker vaccines based on the E2 protein have also been developed. All strains noted have DIVA capability except for the Chinese C strain.

An effective strategy for CSFV vaccination for pig smallholders should consider the following elements:

- Appropriate enabling mechanisms are in place at regional, national and local levels;
    - National policies for pig production, animal identification, regulations and contingency plans for CSF, including zoning and compartmentalization;
    - Laboratory and epidemiological capacity for seromonitoring and virus surveillance programs;
    - On going communication and information sharing among public and private sectors;
    - Risk assessments and cost-benefit studies to evaluate the use of culling and vaccination;
- Evaluate the presence of important immunosuppressive disease agents such as PRRS;
- Utilize the appropriate type of vaccines under the following epidemiological contexts:
    - Free areas of CSFV with Trade Access: emergency vaccination scenarios [34];
    - Endemic Areas: Modified live 'C' type vaccine routine use in endemic areas or alternatively, use of E2 subunit vaccines [34];
    - Emergency Scenarios: Rapid diagnosis and combined use of culling and emergency ring vaccination [40][42];
    - Progressive elimination and freedom from CSFV: development and use of C strain marker vaccines [3].

The key gaps and solutions that need to be addressed prior to developing a potential vaccine:

Short term

- Assess and optimize the existing C strain tissue culture lines for wider use;
- Build vaccine production capacity for thermostable cell culture C strain vaccine based on tissue culture to increase vaccine production capacity, especially in India and Viet Nam;
- Conduct field trials with documented assessments to test the effectiveness of vaccines and diagnostic tests;
- Conduct pilot projects that include education of veterinarians, paraveterinarians and farmers on the proper use and application of vaccines and diagnostic tests.

Medium term

- Support the development of C strain vaccines with DIVA capability with the private sector involvement for cost effective and sustainable eradication of CSF;

- Develop a cheap and effective test kit for virus detection for smallholders to meet the challenge of the predominant genotypes in Asia from the acute form (genotype 1) to the chronic form (genotype 2) which results in silent carriers.
- Conduct epidemiological research and risk assessments in Asia at the interface of commercial pig - smallholder pig production units - wild boar and feral pigs;

Long term

- Further develop subunit marker vaccines that can eliminate all three genotypes;
- Continue basic research immunological properties of all C strain vaccines and subunit marker vaccines;
- Assess needs for oral vaccines for wild and expand the use to backyard pigs in Asia.

Clinical disease overview

Etiology

The CSF viruses primarily affect domesticated pigs and wild boars with variable symptoms according to the virus strain [3][2]. While all CSFV react as a single serotype, they are classified into three major genotypes and ten subtypes (sub-genotypes) [4]. The virion is enveloped, spherical and about 50 nm in diameter.

Virus structure

Classical swine fever virus (CSFV) is a small (12kb), enveloped RNA virus in the genus Pestivirus of the family Flaviviridae. CSFV is antigenically related to the other pestiviruses, including bovine viral diarrhea virus (BVD; including BVDV-1 and BVDV-2) of cattle; to border disease virus (BDV including BDV -1, BDV-2, BDV-3) of sheep; and to a single pestivirus, which was isolated from a giraffe [1][2]. These related pestiviruses are highly prevalent in bovine and ovine populations and can infect pigs. In addition, congenital infections with ruminant pestiviruses in pigs occasionally give rise to a clinical disease that is indistinguishable from classical swine fever (CSF) [2]. The genetic and serotypical characteristics of pestiviruses vary among species.

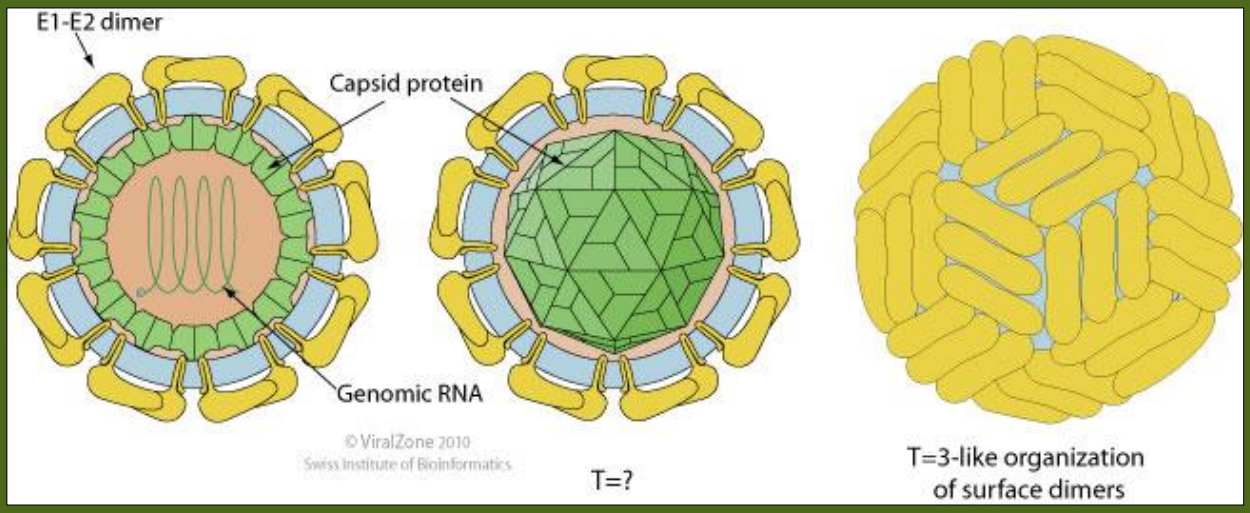


Figure 1: Structure of classical swine fever virus (http://viralzone.expasy.org/all_by_species/39.html)

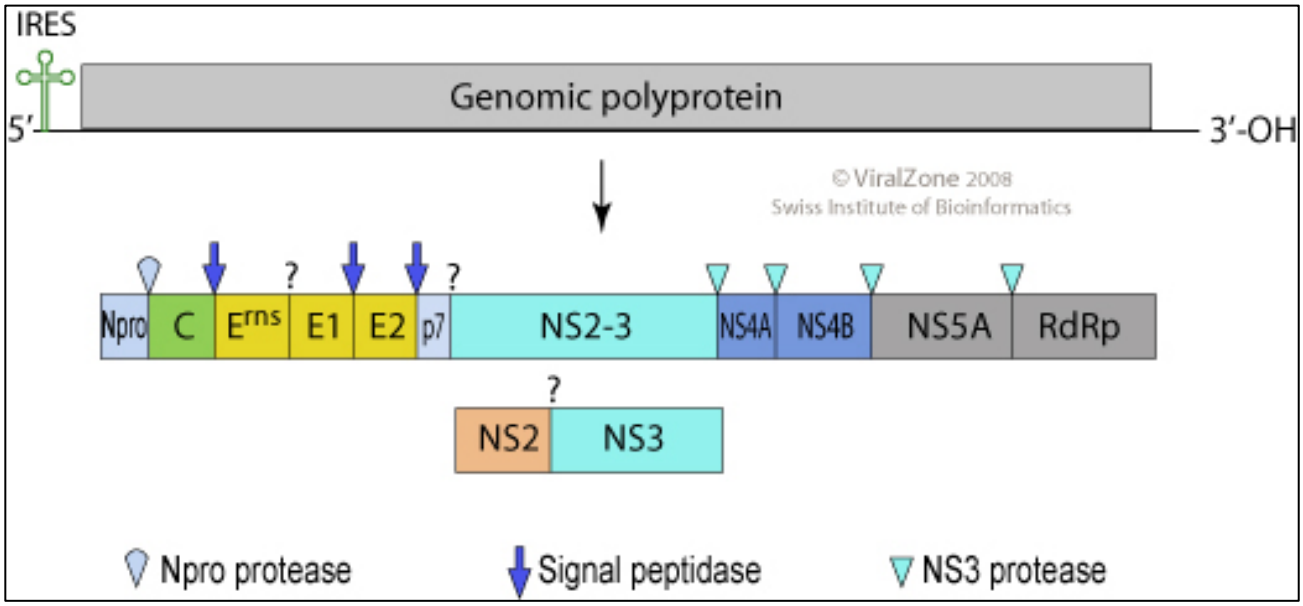


Figure 2: Classical swine fever genome

The genome of CSFV includes 12 proteins arranged in the order in Figure 2 N^{pro} refers to an N^{pro} and E is a glycoprotein with ribonuclease activity. The structural proteins include the capsid protein C and three envelope proteins (E^{rns}, E1, and E2). The E^{rns} (E0) glycoprotein lacks the membrane anchor and is secreted from infected cells and may take part in the initial attachment process of viral entry, rather than in the specific binding or fusion process. The E^{rns} may also play an important role in the post-entry stages, which may be a possible reason causing the CSFV with E^{rns} deletion to be non-transmissible [5]. E2 is the major neutralizing antigen for CSFV infection, while E^{rns} is considered to be the secondary glycoprotein that mediates neutralization [5]. The E^{rns} is unique to *Pestiviruses*, and has been implicated in the evasion of host interferon (IFN) responses [5]. The NTR is most likely involved in initiation of genomic replication as well as being involved in the coordination of the viral translation and replication. The remaining proteins are considered nonstructural and may play an important role in the process of viral replication (NS) [2]. Virus assembly is facilitated by the viral ionic channel p7 and the new virions are released by exocytosis. The key interactions between elements of the virus genome and the host include the attachment of the viral envelope protein E components to host receptors, which initiate entry into the host cell by clathrin-mediated endocytosis. Both E^{rns} and E2 are known to induce viral neutralizing antibodies, which give protective immunity in the pigs [5]. Segregation of pestiviruses into species and subgroups is done on the basis of complete N^{pro} and E2 coding genes and pestiviruses can also be categorized into 7 major groups based on differentiation of the N^{pro} and E genes (Figure 3) [2]. By comparing one-step growth curves of infectious cell-associated and secreted virus from various CSFV strains, one study identified in vitro parameters in PK cell culture correlating with the virulence of the respective virus strain in pigs [6]. The ratio of cell-associated virus versus secreted virus proved to be considerably lower for the highly virulent strains when compared to avirulent or moderately virulent strains [6].

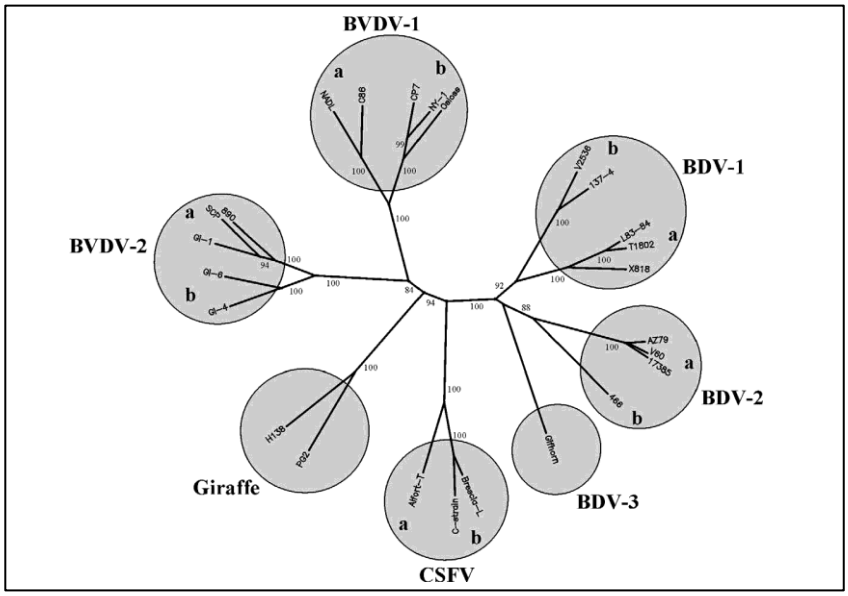


Figure 3: Phylogenetic relationships of pestiviruses (including CSFV) based on N^{pro} and E genes

The CSFV is moderately fragile and does not persist in the open environment. It can survive 3 days at 50°C and 7-15 days at 37°C and is sensitive to drying and ultraviolet light but survives well in pens during cold conditions (up to 4 weeks in winter). The CSFV can survive in pig meat during salt curing and smoking for 17 and for at least 180 days, respectively, depending on the process used. The virus persists 3–4 days in decomposing organs and 15 days in decomposing blood and bone marrow [4].

Epidemiology

CSFV is reported in Europe, Central and South America, the Caribbean and Asia either as an endemically established disease or through epidemics of particular strains, resulting in the death of susceptible pigs and wild boars [7][8]. Table 1 summarizes key epidemiological features of CSF disease to be further explained in greater detail under agent, host and environmental factors below [4].

The first recorded outbreaks of a disease of pigs consistent with classical swine fever or hog cholera occurred in 1822 in France and 1833 in Ohio, USA [7]. These continental epizootics are likely linked via international trade of infected pigs or contaminated imported meat. Eventually CSFV was established in both Europe and North America by the 1860's and by 1903, the transmission via filtrates from infected animals given to susceptible animals was demonstrated. The development and application of a crystal violet inactivated vaccine, an attenuated live virus vaccine and a subunit marker vaccine occurred in 1934, 1951 and 1996, respectively [7].

Table 1: Key epidemiological features of CSF disease

Reservoirs inapparently infected	• The European wild boar acts as non-classical reservoir hosts since they can also be clinically affected depending on the CSFV strain • The role of wild boar in Asia is not established
Natural hosts demonstrating symptoms	• Domestic pigs (*Sus domesticus*), • Feral pigs • Wild boar
Host and vector	• Natural susceptible hosts, including domestic pigs adults and congenitally infected newborns), feral pigs and European wild boar
Transmission	• Oral and oronasal route • Direct transmission between sick and healthy animals • Transplacental transmission to piglets who can become asymptomatic carriers • Human spread – veterinarians, paraveterinarians, pig traders and visitors • Very localized spread via wind within 1km has been recorded • Indirect transmission by feeding waste products material containing infected meat (CSFV can remain infectious for 3–6 months in meat) • Fomites (premises, vehicles, implements, clothes) • Congenitally infected piglets can shed the virus silently for 6-12 months prior to death
Virus sources	• Blood, semen, secretions, excretions and tissues, from inapparently infected adult pigs, sick and dead pigs • Congenitally infected piglets

In 1888, the first cases of CSFV were reported in Japan [7]. In 1996, an eradication program in Japan was initiated in three phases:

Phase 1: A 2-year program was initiated to immunize the pig population by vaccination (as close to 100% as possible);

Phase 2: To establish CSF-free local areas without vaccination and to confirm that the area is free of CSF field viruses;

Phase 3: To suspend vaccination completely and to confirm that the pig population is free of CSF.

Though it was eradicated from Japan, CSFV remains endemic and is reported throughout east, southeast and south Asia. Factors underlying the lack of success in disease control are the lack of funds for vaccination, and in some countries limited expertise and diagnostic facilities to ensure adequate herd immunity [7]. Currently, CSF still occurs sporadically or remains endemic in many regions of China [9].

The incubation period of CSFV in the pig host is 2-14 days [1][4]. Following ingestion in the pig host, the CSFV replicates in the tonsils and through the regional lymph nodes, after which viral shedding from faces and urine begins 6-9 days post-infection [10]. The natural infection route is oronasal although conjunctival, genital and parenteral routes also exist. The minimal amount of viral particles required for infection is route-dependent and low viral doses (up to 10 TCID50) are sufficient [10]. The virus can survive in the environment, for three days at 50°C and for 7-15 days at 37°C. It can survive for years at -70°C. The CSFV can survive for 90 days in frozen meat and 188 days in ham [11]. Rapid temperature changes are harmful. It can survive between 4 days and 4 weeks in manure depending on temperature and other environmental factors [11].

Both direct and indirect transmission of CSFV are important mechanisms for its spread. Direct transmission can be from horizontal and vertical transmission. Indirect transmission occurs via humans, transport vehicles, artificial insemination and fomites [10]. The Basic Reproductive Number (R_0) is a mathematical ratio, which describes the rate of secondary disease spread from following a primary case. For example, an R_0 of 4 indicates that each primary case generates 4 secondary cases. Table 2 summarizes R_0 values for CSFV transmission under various epidemiological contexts [10][12][13].

Table 2: R_0 values for CSFV transmission under various epidemiological contexts

R_0 values (95% CI)	**Context**	**References**
100 (54.4–186)	Weaner pigs within-pen estimate in an intensive production system	Klinkenberg et al., 2002 [12]
7.77 (4.68–12.9)	Weaner pigs between-pen estimate in an intensive production system	Klinkenberg et al., 2002 [12]
15.5 (6.20–38.7)	Slaughter pigs within-pen estimate	Klinkenberg et al., 2002 [12]

3.39 (1.54–7.45)	Slaughter pigs between-pen estimate	Klinkenberg et al., 2002 [12]
13.7	Experimental pigs in a pen	Laevens et al., 2013 [13]
13.0	Gilts in a pen	Dewulf et al., 2001
1.7	Wild pigs in their natural environment	Hone et al., 1991

From Table 2 it is evident that the distance between infected and susceptible pigs, the contact rate, dose received and host factors influence the rate of transmission. At the population level, direct contact can be significant risk for the transmission of CSFV. During the high-risk period of the Dutch outbreak in 1997-1998, 17% of the between-herd virus spread was due to direct contact [10]. In addition, eating raw pork meat is a common cultural practice in tribal areas of some Southeast Asian countries, permitting uneaten waste meat to become available for domestic as well as wild pigs to feed upon. A summary of risk factors for the introduction and spread of CSFV has been compiled by the OIE, and is presented in Table 3 [14].

The main risks for transmission of CSFV include the movement of pigs, which are incubating the disease, or are persistently infected; indirect spread of virus through transport vehicles; human contacts; and feeding pork waste, which has not been properly heated. Classical swine fever virus can survive in pork and pork products after processing [14]. The presence of virus in infected wild boar is an important risk factor either through direct live contact or indirect contact, including feeding infected uncooked meat to susceptible pigs. Mechanical transmission over short distances (neighborhood effect) by wind aerosols, arthropod vectors, birds, pet animals and rodents has sometimes been reported as well as transmission by manure and by contaminated semen through artificial insemination practices [14].

Table 3: Risk factors associated with introduction and spread of CSFV (Adapted from de Vos et al., 2003)

Transmission route	Importance for introduction	Importance for spread
Animal movements	++	++
Transport vehicles	+	++
Human contacts	+/–	++
Swill-feeding	++	+/–
Wild boar	++	–
Air currents	–	+/–
Rodents, birds, arthropods, pets	–	+/–
Manure	–	+/–
Genetic material	+/–	+

– : unimportant
+/–: might be important
+ : important
++ : very important

a) A selection of references has been made. An extensive overview of references can be obtained from the corresponding author

Agent Factors

The CSFV is categorized into three major genotypes containing 10 sub-genotypes as defined by the E2-gp gene fragment depicted in Figure 4 [15].

Interestingly, the only African CSFV isolate detected in South Africa belongs to Group 2.1, and is related to isolates from Asia and Europe. The molecular epidemiology of this lone African isolate suggests an epidemiological link related to trade with these other regions. In addition, the evolution of Group 3 is clustered in the Asian region thus far. Phylogenetic analysis of the Korean field isolates of 1988 - 1999 fall under subgroup 3.2, however the viruses isolated during the 2002-2003 CSF epidemics belong to a different group [16]. Beer et al. have summarized the global spatial distribution of CSFV sub-genotypes as presented in Figure 5 [17]. CSFV isolates from Asia were also classified by Geiser-Wilke and Paton, which are summarized in Table 4 [18].

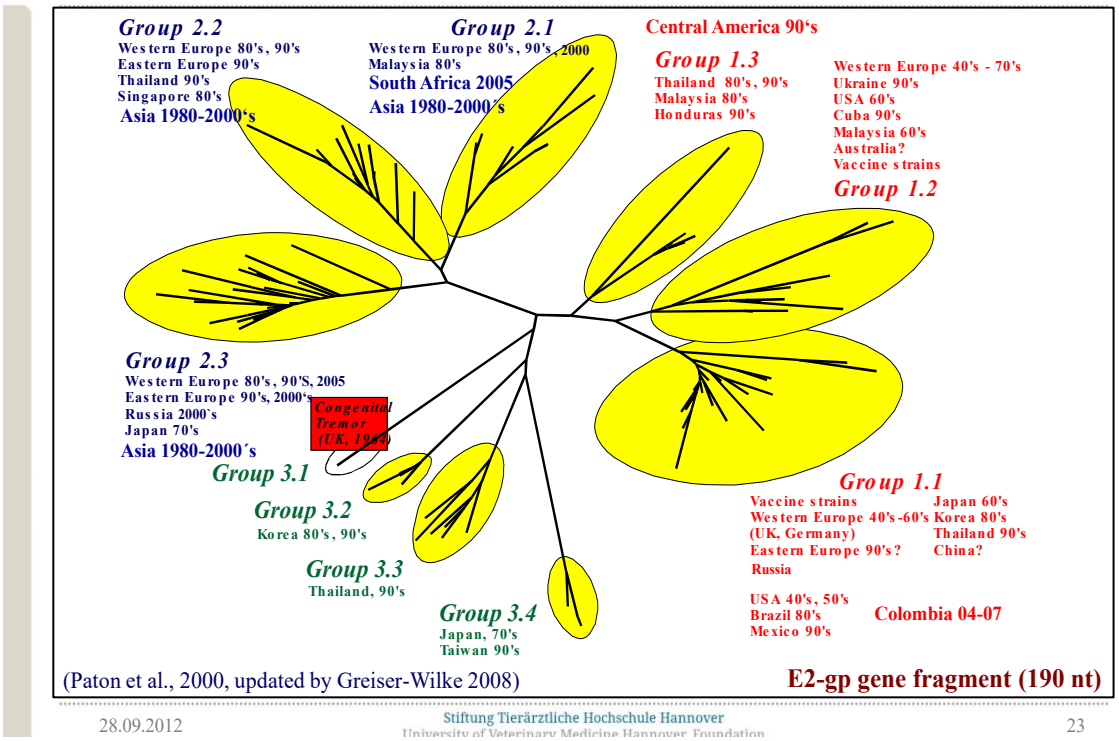


Figure 4: Genetic diversity of CSFV into 10 sub-genotypes as defined by the E2-gp gene fragment

Figure 5: Global spatial distribution of CSFV sub-genotypes

Table 4: Distribution of CSFV sub-genotype groups isolated in Asia

Sub-genotype Group	Country	Epidemiological Relevance	Reference
1.1	Hokkaido, Japan	1996 isolate	[18]
2.3	Osaka, Japan	1971 isolate	[18]
1.1	Thailand	1980's	Lowings et al. 1996: Parchariyanon et al. 2000
1.2	Thailand and Malyasia	1980's	Lowings et al. 1996: Parchariyanon et al. 2000
2.1	Austria	Wild boar meat imported into Austria from China	Hofrilann and Bossy 1998
2.2	Thailand	1990's	[18]
1.3	Thailand and Malaysia	New cluster developed from isolates found in 1980's and 1990's	[18]
3.2	Korea	1980's and 1990's	[18]
3.3	Thailand	1990's	[18]
3.4	Japan and Taiwan	1890's and 1990's	[18]

Viet Nam has the largest pig population in Southeast Asia where 70% of the 27.4 million pigs (2010) are raised in smallholder production units [19]. In Viet Nam, Tung et al. conducted a study on 44 CSFV isolates from the country along with 271 reference viruses and found that a single sub-genotype 2.1c of CSF virus was dominant in the north Vietnam in 2010, while Dung, et al. had reported the presence of both sub-genotype 2.1 (8 isolates) and 2.2 (10 isolates) in the same region in 2003 [20]. In the neighboring Lao People's Democratic Republic (PDR), genotype 2.1 is found in the north-central region while genotype 2.2 is found in the south-central region [21]. Figure 6 presents a map of the locations for these two genotypes in Lao PDR.

CSFV is also a significant disease in South Asia where molecular research is being actively pursued. The molecular epidemiology of Indian and Nepali CSFV isolates from this region is summarized in Table 5 [16][17].

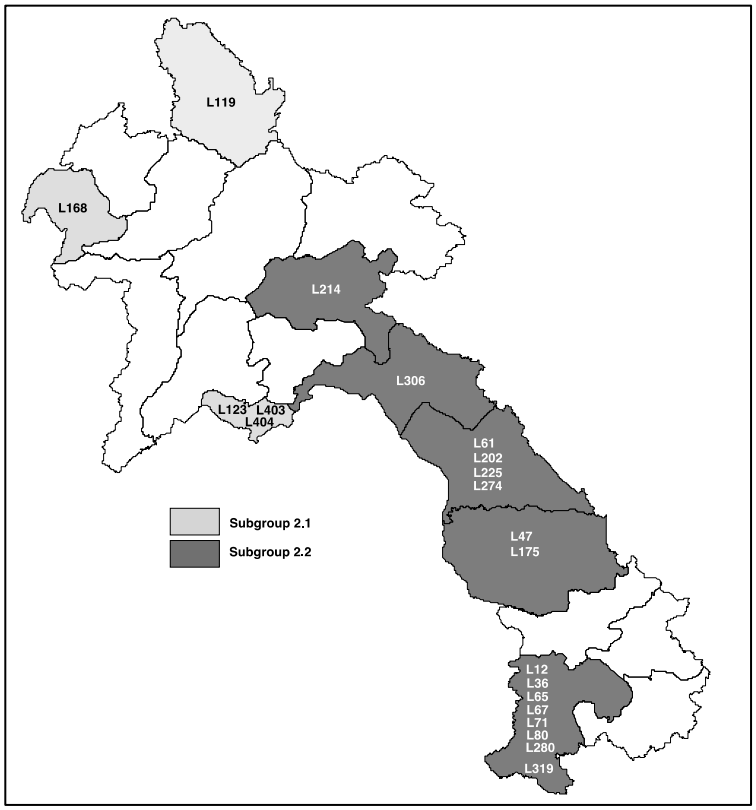


Figure 6: Map of Lao PDR depicting the locations of CSFV genotypes 2.1. And 2.2

Table 5: Distribution of CSFV sub-genotype groups isolated in Indian States and in Nepal

Sub-genotype Group	Indian State/Country	Epidemiological Relevance	Reference
1.1	Uttar Pradesh	Immunogenic vaccine seed strain	Singh et al. 2006
Strain Shimen-HVRI	Mizoram State	Related to isolates from Myanmar and China	Barman et al., 2010
2.1	Survey of various Indian States	Related to European strain	Desai et al., 2010

1.1	Assam	190 isolates from field outbreaks characterized using E2 gene fragment	Patil et al., 2011
2.1	Assam		Ahuja, 2015
2.2	Karnataka	Analysis of NTR gene region	Chakraborty et al., 2011
2.2	Uttarakhand	First whole genome sequence of 2.2 in India	Kumar et al., 2014
2.2	Nepal	Part of endemic cycle and closely matches Indian CSFV isolates	Postel et al., 2013

Lowings et al. assessed the evolution of CSFV sub-genotypes to occur at a rate of 1-9 x 10^{-3} to 9.3 x 10^{-3} substitutions per base per year [22]. Another study used the Bayesian statistical analysis to study the evolution of the NS4B gene fragment of 37 isolates and determined an evolutionary rate of 13 × .010^{-4} substitutions per site per year [23]. The E2 segment was demonstrated to give the greatest resolution with the greatest statistical confidence.

Host Factors

Wild boar in Europe play a role as reservoirs but not in the classic sense since transmission among European wild boar is very limited. However the European wild boar remains an important source for domesticated pigs in Europe [11]. Limited epidemiological data currently exists regarding the role of wild and feral pigs in Asia.

Virus-host interaction is critical in order to understand the epidemiology of CSFV in pig populations. Experimental studies using a single commercial genetic line of pigs demonstrates that the virulence of CSFV isolates is highly variable and young pigs are more susceptible to CSFV. For CSF, the clinical and pathological scoring criteria is based on case fatality rate, antibody production and leukocyte count [24]. A molecular genomic study of 52 isolates found that CSFV virulence could not be linked to any particular genome sequence [25]. Most of the highly virulent CSFV strains belong to genotype 1 which also includes the vaccine strains. Moderately virulent strains belong to genotypes 2 and 3. There is evidence that genetic variability within the genotype 1 is lower compared to strains of genotype 2 and 3. The study presents the hypothesis that sequence signatures of virulence may be found using the full sequence data of vaccine strains and parental highly virulent strains [25]. However, from the functional point of view, virulence may depend on viral replication efficiency, which can be influenced by differences in protein expression and other host-agent interactions.

Genetic differences with the pig population influence the transmission and temporal dynamics of CSFV outbreaks. Blacksell et al., investigated in Lao PDR the susceptibility of indigenous *Moo Laat* (ML) and improved Large White/Landrace cross (LWC) pig breeds to infection with CSFV under controlled conditions [26]. This study generated a survival analysis of both breeds as shown in Figure 7. The following conclusions from this study indicate that:

- Native breed and an improved pig breed are fully susceptible to CSFV infection and the mortality rate is high.
- LWC pigs demonstrated lower (or shorter) survival times (50% survival time: 11 days), earlier and higher pyrexia and earlier onset of viraemia compared to ML pigs (50% survival time: 18 days).
- In the context of village-based pig production, the longer time from infection to death in native ML pigs means that incubating or early sick pigs may increase and prolong transmission of CSFV since they are likely to be sold once an outbreak of CSF is recognized in a village.
- This increased longevity probably contributes to the maintenance and spread of disease within a population where generally the contact rate is low.

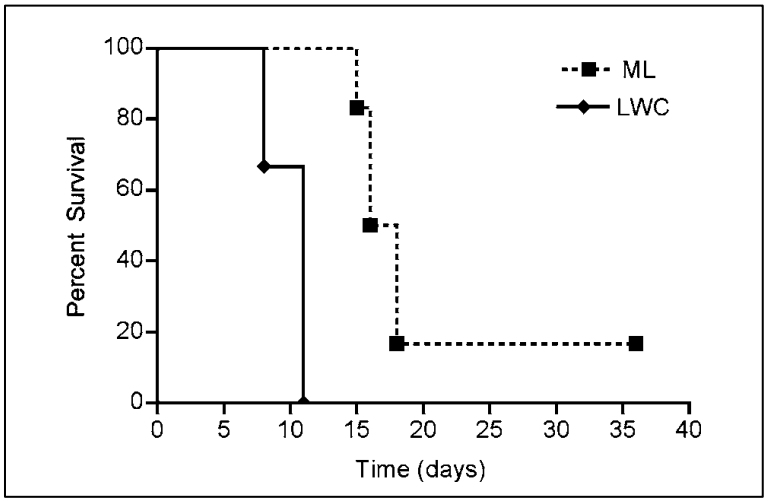


Figure 7: Survival characteristics of CSFV in Moo Laat and Large White/Landrace cross breeds from Lao PDR

Virus excretion for mild moderate and highly virulent strains differ. Weesendorp et al., conducted a study to measure the excretion of CSFV over time from pigs infected with a high, moderate or low virulence strain. The study measured clinical signs, conducted RT-PCR analysis as well as virus titration from conjunctival fluid, nasal fluid, faces and urine for 56dpi. The study highlights the crucial role chronically infected pigs play in the transmission of CSFV as summarized below [27]:

1. Infectious virus was excreted in all secretions and excretions of pigs infected with the highly and moderately virulent strain, while excretion from pigs infected with the low virulent strain was mostly restricted to the oronasal route;

2. Pigs infected with the highly virulent strain excreted significantly more virus in all their secretions and excretions over the entire infectious period compared to pigs infected with the moderately or low virulent strains. However this prolonged high level shedding did not occur in the pigs that developed the chronic form of infection after inoculation with the moderate virulence strain;

3. During the entire infectious period, infected pigs excreted the largest amounts of virus via most secretions and excretions, as they excreted virus continuously and for a long duration.

Congenital infection through transplacental infection from a carrier sow is another critically important mechanism for the persistence and transmission of CSFV. The infected foetus can die in utero, in the neonatal period, or it may be born with teratogenic defects. In addition, apparently healthy progeny can develop a late onset disease, months, or years after birth, or remain clinically normal for life. The outcome of a congenital infection is mainly determined by the stage of fetal development at which the infection occurs [28]. If the infection occurs during the first trimester, before the fetuses have developed immune competence, it can result in the birth of persistently infected piglets. These piglets are born asymptomatic and without antibodies to CSFV. They then shed virus intermittently until they develop clinical signs of acute CSF and die up to 11 months later [29].

The ability of two CSFV field isolates of low and moderate virulence to induce viral persistence after early postnatal infection has been evaluated [30]. Two litters of 10 piglets each were infected intranasally on the day of birth with low and moderate virulence CSFV isolates, respectively. During the six weeks after postnatal infection, most of the piglets remained clinically healthy, despite persistent high virus titers in the serum. Importantly, these animals were unable to mount any detectable humoral and cellular immune response. At necropsy, the most prominent gross pathological lesion was severe thymus atrophy.

Finally, Figure 8 summarizes the epidemiological features for the transmission of CSFV from piglets infected during the neonatal period either acutely or chronically [15]. Note that virus shedding is prolonged and antibody production is suppressed in chronically infected piglets.

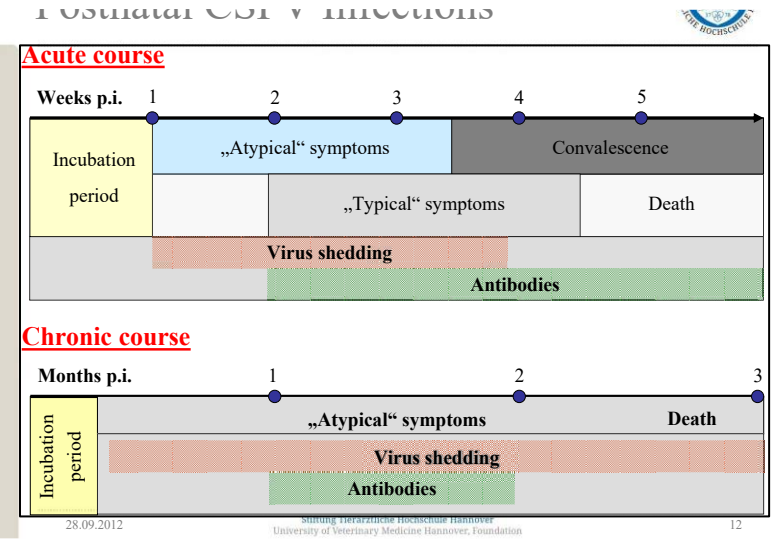


Figure 8: Model experiments for acute and chronic from postnatal infections in piglets

Environmental Factors

Weesendorp et al. conducted a study to quantify aerosol spread of CSFV under experimental housing conditions [31]. They used highly virulent strains with titers of $10^{1.2}$ to $10^{3.0}$ TCID50/m^3 of infectious virus and $10^{1.6}$ to $10^{3.8}$ TCID50 equivalents/m^3 of viral RNA. They observed that the higher the dose used for inoculation of the pigs, the sooner virus could be detected in the air samples. There is also a moderate relationship between infectious virus titer in the air and the number of pigs excreting infectious virus in faeces (Spearman's rank correlation coefficient 0.67, p=0.005) or oropharyngeal fluid (Spearman's rank correlation coefficient 0.57, p=0.014). No infectious virus or viral RNA was detected with the low virulence strain, indicating that the level of aerosols released corresponds to the virulence levels of CSFV.

The ecological carrying capacity, food availability across the interface between the wild and feral pigs with the domesticated pigs in the smallholder village setting also affects the rate of contact and likelihood of introduction and transmission in the population [11]. Human behaviour such as hunting feral and wild pigs and feeding their uncooked parts to domestic pigs is also a risk at the interface noted above.

Clinical Signs

The clinical signs of CSFV are not pathognomonic and are based on whether the infection with CSFV is the acute form, the chronic form or the congenital form. The precise signs and symptoms will also vary due to the host

characteristics (genetics, age, previous exposure) including the virulence of the specific CSFV involved. Based on the OIE definitions, the clinical signs associated with CSFV in pigs are summarized in Table 6 [3][4].

Table 6: Clinical signs consistent with the four forms of CSFV

Acute	Chronic	Congenital	Mild
Virulence			
Virulent virus strains and/or younger pigs	Less virulent virus strains or partially immune herds	Depends on virulence of virus strain and stage of gestation	Mild in older pigs
Mortality			
Mortality in young pigs can approach 100%	Moderate	Variable up to 100%	Low
Time until death			
5–25 days after onset of illness	Apparent recovery with eventual relapse and death in 3 months	Within weeks or up to 12 months	Long time period
Clinical signs			
• Fever (41°C) • Anorexia, lethargy • Severe leucopenia • Multifocal hyperaemia and/or haemorrhagic lesions of the skin • Conjunctivitis • Enlarged, swollen lymph nodes • Cyanosis of the skin especially of extremities (ears, limbs, tail, snout)	• Dullness, capricious appetite, pyrexia, diarrhoea for up to 1 month • Ruffled appearance of pigs • Growth retardation	• Fetal death, resorption, mummification, stillbirth • Abortion • Congenital tremor, weakness • Runting and poor growth over a period of weeks or months	• Transient pyrexia and inappetence

• Transient constipation followed by diarrhoea • Vomiting (occasional) • Dyspnoea, coughing • Ataxia, paresis and convulsion • Pigs huddle together			
Epidemiological significance			
Rapid short term onset, virus multiplication and transmission in single age herd; more prolonged in multi-age smallholder setting	Prolonged virus multiplication and shedding	Born clinically normal but persistently viraemic with no antibody response: important intermittent shedders of virus	Recovery with lifelong immunity

Diagnosis

The OIE advises that *"A tentative diagnosis based on clinical signs and post-mortem lesions must therefore be confirmed by laboratory investigations. As pyrexia is one of the first signs of CSF and is accompanied by viraemia (Depner et al., 1994), detection of virus or viral nucleic acid in whole blood, collected in heparin or ethylene diamine tetra-acetic acid (EDTA), or in tissues, collected from febrile animals, is the method of choice for detecting infected herds at an early stage."* [3]

Laboratory methods for diagnosis of CSF are aimed at detection of: 1) the virus; 2) viral nucleic acid or viral antigens; or 3) detection of specific antibodies. Targeted and risk-based sampling of animals is recommended as follows [2]:

- When no clinical signs of disease are present: random sampling is applied;
- When diseased animals and febrile animals are present: Detection of virus, viral antigen or nucleic acid;
- To verify previous exposure: Detection of antibodies from animals that have recovered from disease or animals that have been in contact with infected or diseased animals persist for life [4].

Differential Diagnosis

There are two challenges in the diagnosis of CSFV. Firstly, the clinical signs of classical swine fever are similar to a number of other swine diseases. Secondly, the diagnostic tests used must be able to differentiate CSFV from bovine viral diarrhea (BVD) and other pestiviruses.

The differential diagnosis of CSFV considered will vary depending on the form of the CSF disease, including acute, chronic, congenital (and mild forms). It is therefore essential to send samples for laboratory confirmation. Important categories of clinical symptoms for other diseases, which may resemble the various forms of classical swine fever, are summarized in Table 7 [4]:

Table 7: Differential diagnosis of CSF

African swine fever: A primary differential diagnosis to rule out with indistinguishable clinical signs and pathological lesions;
Septicaemias with skin lesions: erysipelas, eperythrozoonosis, salmonellosis, streptococcosis, pasteurellosis, actinobacillosis, and Haemophilus parasuis;
Haemorrhage: porcine dermatitis and nephropathy syndrome, haemolytic disease of the newborn, coumarin poisoning, thrombocytopenic purpura;
Runting: post weaning multisystemic wasting syndrome, enterotoxicosis, swine dysentery and campylobacteriosis;
Abortion: Aujeszky's disease (pseudorabies virus), encephalomyocarditis virus infection, porcine reproductive and respiratory syndrome, parvovirus;
Nervous signs: viral encephalomyelitis, salt poisoning;
Congenital infection with ruminant pestiviruses: Bovine virus diarrhea, Border disease

Gross pathology or gross lesion at post-mortem

Gross post mortem lesions associated with CSFV are not pathognomonic. Lesions in the following organ systems must be further investigated with laboratory tests when they are found. Table 8 presents a summary of gross pathological changes associated with the three main forms of ASF disease resulting in pathological lesions.

Table 8: Gross pathological changes associated with the four forms of ASF disease

Body system	Acute form	Chronic form	Congenital form
Haematopoietic	Leucopoenia and thrombocytopenia; Multifocal infarction of the margin of the spleen		
Integumentary	Petechiael and ecchymotic haemorrhages		
Nervous	Encephalomyelitis with perivascular cuffing is common		Central dysmyelinogenesis, cerebellar hypoplasia, microencephaly,
Digestive	Petechiael and ecchymotic haemorrhages	Button' ulcers in the caecum and large intestine mucosa	
Renal	Petechiael and ecchymotic haemorrhages		
Respiratory	Lungs may be congested and haemorrhagic		Pulmonary hypoplasia
Lymphatic	Enlarged haemorrhagic lymph nodes are common; Severe tonsillitis with necrotic foci	Generalized depletion of lymphoid tissue	
Reproductive			
Musculo-skeletal		Transverse striations of unmodelled growth cartilage at costochondral junctions in growing pigs	
Miscellaneous			Hydrops and other malformations

Diagnostic Tests

The method of choice for detecting herds early in infection is to collect whole blood and tissues from febrile or recently dead animals. Recommended tissues to collect include tonsil, lymph nodes (pharyngeal, mesenteric), spleen, kidney, distal ileum, blood in EDTA or in Heparin tubes (live cases). The OIE specifies the following tests for the detection and confirmation of CSFV [3]:

Identification of the agent:

1. **VI:** The definitive test

In the laboratory, CSFV from organs, leukocytes or whole blood is cultured in the PK-15 cell line (porcine kidney). Presence of the CSFV does not generally cause a visible cytopathic effect [1]. The presence of CSFV must be demonstrated by an immunostaining method, which may be carried out after one or two virus passages. This can be done by examining the cultures for fluorescent foci by the FAT after 24–72 hours or by immunoperoxidase staining after 3–4 days of incubation. The specific test protocols are provided for the following matrices:

   a. Protocol 1: Tissue samples from dead pigs;

   b. Protocol 2: Whole blood from sick pigs (less sensitive but earlier detection possible from clinical cases);

   c. Protocol 3: Two passages in PK-15 cells will increase sensitivity to detect CSFV in both organ and blood samples.

   d. Protocol 4: RT-PCR provides results quickly with high sensitivity;

   e. Protocol 5: CSFV RNA followed by nucleotide sequencing permits the study of the molecular epidemiology of CSFV following RT-PCR.

2. **Immunological methods:** Provide presumptive but requires confirmation by virus isolation or RT-PCR when negative results are obtained.

   a. FAT of tissue samples. RT-PCR is required to differentiate infected from vaccinated pigs;

   b. Immunoperoxidase procedure for differentiation of pestiviruses by monoclonal antibodies and for the differentiation of infected from vaccinated pigs. Figure 9 presents the systematic approach for interpretation of the Immunoperoxidase procedure for CSFV noted above.

   c. Antigen-capture assay for rapid diagnosis of CSF in live pigs, antigen-capture ELISAs have been developed for screening herds suspected of having been recently infected.

In addition, Aguerro et al. have developed a highly sensitive and specific one-step hot start multiplex RT-PCR assay for the simultaneous and differential diagnosis of African swine fever virus (ASF) and CSFV [32]. Universal detection of ASF and CSF virus strains was achieved through selection of primers in conserved viral genome regions through a study of 150 positive field samples from several ASF and CSF outbreaks validated the suitability of this method for a rapid, sensitive and specific differential diagnosis in clinical samples.

Table 9: Interpretation of the Immunoperoxidase procedure for CSFV

Polyclonal antibody	Monoclonal antibody specific for			Interpretation
	CSF strain	CSF vaccine strain	BVD/BD strain	
+	+	–	–	CSF field strain
+	+	+	–	CSF vaccine strain
+	–	–	+	BVD/BD strain
+	–	–	–	Other non-CSF *Pestivirus*[†]

[†]The existence of novel strains of CSF should always be considered and any isolate from cases where CSF is still suspected should be sent to an OIE Reference Laboratory.

Serological tests:

Due to the immunosuppressive effect of CSFV, antibodies cannot be detected with certainty until at least 21 dpi. The following tests are applied:

1. **NPLA** is a prescribed test for international trade;
2. **FAVN** is a prescribed test for international trade;
3. **ELISA** is a prescribed test for international trade.

The OIE official diagnostic test methods for the diagnosis of classical swine fever and their purpose are presented in Table 10 [3].

Zoonotic disease

Classical swine fever virus is species-specific for pigs and is not considered to be a zoonotic disease [1][3][4].

Table 10: The OIE approved diagnostic tests for CSFV and their purpose

Method	Purpose					
	Population freedom from infection	Individual animal freedom from infection prior to movement	Contribute to eradication policies	Confirmation of clinical cases	Sero-prevalence of infection – surveillance	Immune status in individual animals or populations post-vaccination
Agent identification[1]						
Virus isolation	–	+	–	+++	–	–
PCR	+	+	++	+++	++	–
ELISA (antigen)	++	+	+	+	–	–
FAT	–	–	+	+	–	–
Detection of immune response[2]						
ELISA (antibody)	+++	+++	+++	–	+++	+++
VN (FAVN or NPLA)	+	+++	++	++	+++	+++

Key: +++ = recommended method; ++ = suitable method; + = may be used in some situations, but cost, reliability, or other factors severely limits its application; – = not appropriate for this purpose.
Although not all of the tests listed as category +++ or ++ have undergone formal validation, their routine nature and the fact that they have been used widely without dubious results, makes them acceptable.
PCR = polymerase chain reaction; ELISA = enzyme-linked immunosorbent assay; VN = virus neutralisation; FAT = fluorescent antibody test.

Incidence and Prevalence in Selected Countries

Global

Regionally, the most active areas of reported CSFV events during the first six months of 2015 were Southeast Asia and South Asia including Nepal. The lack of reporting from India is likely due to late reporting since: i) Nepal is affected and cross border trading is ongoing with India; and ii) reports since 2000 consistently show a significant number of reported cases (see incidence Table 12 below). The OIE map of reported CSFV globally is presented in Figure 9. However, only countries coloured green in Figure 10 are recognized as officially free of CSFV

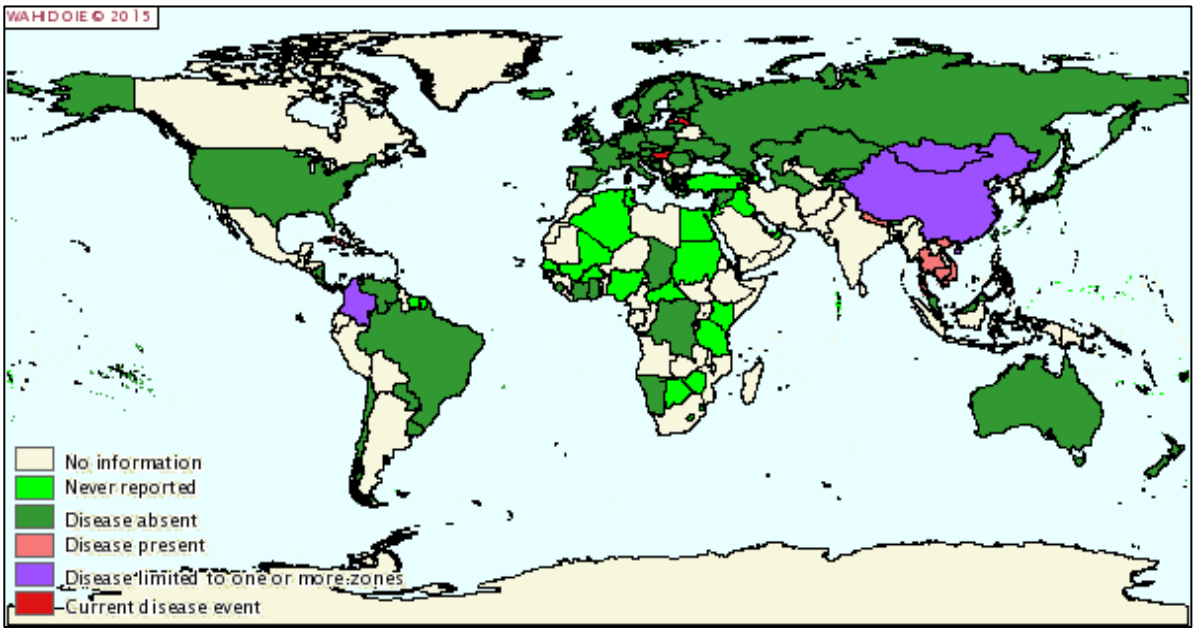


Figure 9: OIE map of reported CSFV

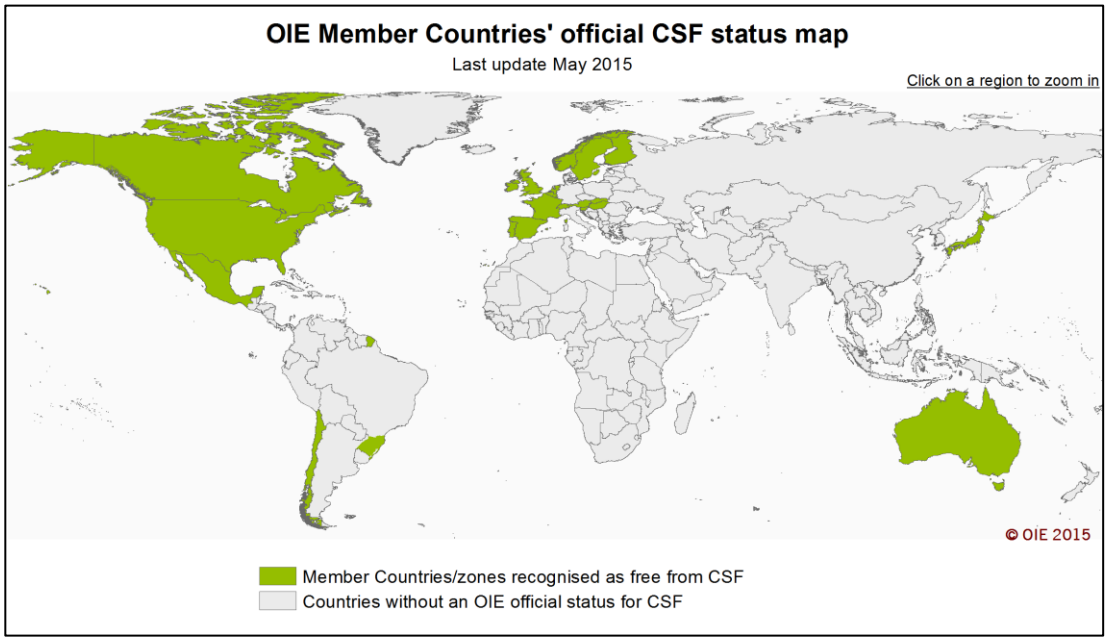


Figure 10: Global status of CSFV Free Countries as of May 2015

However, uncertainty remains with respect to the status of CSFV in Africa. Table 11 summarizes the reporting status of CSFV in the 14 African countries included in the 20 selected countries of the Livestock Vaccine Innovation Fund (LVIF) [33].

Table 11: Ten leading disease losses globally by livestock disease units (LSU) loss

Country	Status	Reference
Burkina Faso	Disease never reported	OIE, 2009
Côte d'Ivoire	Disease not reported	OIE Handistatus, 2005
Ethiopia	No information available	OIE, 2009
Kenya	Disease never reported	OIE, 2009

Madagascar	Present	OIE, 2009
Malawi	Disease never reported	OIE, 2009
Mali	No information available	OIE, 2009
Mozambique	Disease never reported	OIE, 2009
Rwanda	No information available	OIE, 2009
Senegal	Disease never reported	OIE, 2009
South Africa	Disease not reported	OIE, 2009
Tanzania	Disease never reported	OIE, 2009
Uganda	No information available	OIE, 2009
Zambia	Disease never reported	OIE, 2009

Madagascar became infected with CSF by the introduction of infected pigs from Europe in 1965 and the disease has been endemic ever since [34]. South Africa was affected by CSF between 2004 and 2007 when it was eradicated through a challenging culling campaign of a half million pigs. The South African outbreak was linked to food waste from a ship traveling from Asia and not to neighbouring countries. Experimental evidence supports the hypothesis that bush pigs were severely affected and died rapidly and so would be unlikely to become a reservoir host. However warthogs were less severely affected, with non-specific clinical signs and pathological lesions and could potentially act as a reservoir host [34].

A summary of the incidence of CSFV and the prevalence of CSFV between 2000 and 2015 in the 20 selected countries of the LVIF is presented in Table 12 and Table 13, respectively.

Regional

Incidence of CSFV in 20 Selected Countries

Table 12: Annual incidence of CSFV in 20 selected countries, 2000 to 2015.

Region/Country	Reported Incidence CSF (OIE, WAHID) http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail# (Accessed 21/10/2015)															
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Sub Saharan Africa																
Burkina Faso	0	0	0	0	0	…	0	0	0	0	0	0	0	0	0	…
Ethiopia	0	0	0	0	0	…	…	…	…	0	0	?	?	0	0	…
Ivory Coast	0	0	0	0	0	0	…	…	0	0	0	0	0	0	0	0…
Kenya	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0…
Madagascar	3	…	27	16	17	5	6	…+	…+	…+	7	2	2	4	4	…
Malawi	0	0	0	0	0	0	0	0	0	0	0	0	0	0	…	…
Mali	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	…
Mozambique	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	…

Rwanda	…	…	…	…	0	…	0	0	0	0	0	0	0	0	0	…
Senegal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0…
South Africa	0	0	0	0	0	68	22	1	0	0	0	0	0	0	0	0…
Tanzania	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0…
Uganda	0	0	0	0	0	0	…	…	…	…	…	…	…	…	…	…
Zambia	0	0	0	0	0	…	0	0	0	0	0	0	0	0	0	…
South Asia																
Bangladesh	…	0	0	0	0	…	…	0	0	0	0	0	0	0	…	…
India	5	236	190	53	59	54	40	93	95	136	418	284	252	117^	69	…
Nepal	5	12	31	15	6	19	23	30	8+	29	14	34	10	6	9	2…
Southeast Asia																
Indonesia	…	…	…	…	…	…	…+	…+	…+	…+	…+	…+	…+	…+	…	…
Myanmar	4	10	0	1	2	…+	2+	1…+	3	0	0	0^	0	2	3	…
Vietnam	…	…	…	58	…	221	364	337	650	171	214	68	128	80	65	24…
Legend: ^PRRS First Reported																

WAHIS Codes 2005-2015

...	No information available for this disease
0	Disease absent
...+	Disease present but without quantitative data

HandiStatus II Codes 2000-2004:

...	No information available
0	Disease absent

Prevalence in 20 Selected Countries

Table 13: Prevalence estimates for CSFV in 20 selected countries based on the available peer-reviewed studies

Region/Country	Apparent Prevalence (CI)	Study Design	Time Period	Reference
Sub Saharan Africa				
Burkina Faso				
Ethiopia				
Ivory Coast				

Kenya				
Madagascar				
Malawi				
Mali				
Mozambique				
Rwanda				
Senegal				
South Africa	Serological surveys in domestic pigs and a limited number of warthogs sampled have yielded no positive samples since October 2007 and national surveillance gave no indication of spread to other provinces.	Prospective serological surveys in the Eastern Cape	2007-2010	Akol and Lubisi ,2010
Tanzania				
Uganda				
Zambia				
South Asia				
Bangladesh				

India	Seroprevalence was 41% (89/218) and prevalence of CSFV antigen in blood samples was 32% (39/121) for the 10 districts of Karnataka. Seroprevalence of 61%, 29%, 20%, and 21%; and antigen prevalence of 40%, 50%, 13%, and 12% were recorded for Bangalore, Mysore, Belgaum, and Gulbarga divisions of Karnataka, respectively.	Prospective serological and antigen capture ELISA based survey in selected districts and divisions of Karnataka State	2013-2014	Choori et al., 2015
	CSF seroprevalence of 63% from 12 different states of India during 2004-2010 and 53% prevalence in Southern India alone.	Prospective serological survey	2004-2010	Nandi et al., 2011
	Seroprevalence of CSF in Kerala and Tamil Nadu to be approximately 77% (31/40) and 100% (10/10), respectively	Prospective serological survey	2012-2013	PD_ADMAS. 2013
	The prevalence of CSF antibodies from serum samples for the whole of Karnataka was 33% (173/517) in 20 districts	Prospective serological survey	2014	Shivaraj et al., 2014

Nepal	Out of 233 outbreaks since 2002, 143 (61.37%) and 90 (38.6%) were reported from hill and terai (lowland) regions, respectively. None reported from the mountain region.	Geographic distribution of CSFV outbreaks in Nepal	2002-2014	Proceedings of 1st National Workshop on Pig and Pork Industry in Nepal, 2014
Southeast Asia				
Indonesia	17.8% (95% CI: 15.1-20.8%) of the pigs were seropositive to CSF.	Prospective serological survey involving 720 pigs	2010	Bulu, 2011
	30.9% seropositive	Prospective serological survey	NA	Santhia *et al*. 2001
	seroprevalence was estimated at 17.5% (lower CI 16.0%; upper CI 19.5%).	Cross-sectional seroprevalence survey was conducted in 2010 involving 2,160 pigs and 805 farmers from four islands in the region.	2010	Sawford et al., 2015
Myanmar				
Vietnam	All 10 farms with mortality were positive by RT-PCR test; Antibody against CSF virus was not detected in 7 of 10 herds during an outbreak of CSF.	Cross-sectional study during an active outbreak in Cantho Province	2002-2003	Kamakawa et al.

Conclusions

There were a total of 4,938 CSFV events reported by the 20 selected countries investigated by the LVIF between 2000 and 2015. Forty-eight per cent (48%) of all CSFV events were reported in Viet Nam while 42% were reported in India. Nepal (5%), Madagascar (2%), South Africa (2%) and Myanmar (1%) accounted for the remainder of reported events during the same time interval. Figure 11 provides an ordered ranking by number of CSFV events.

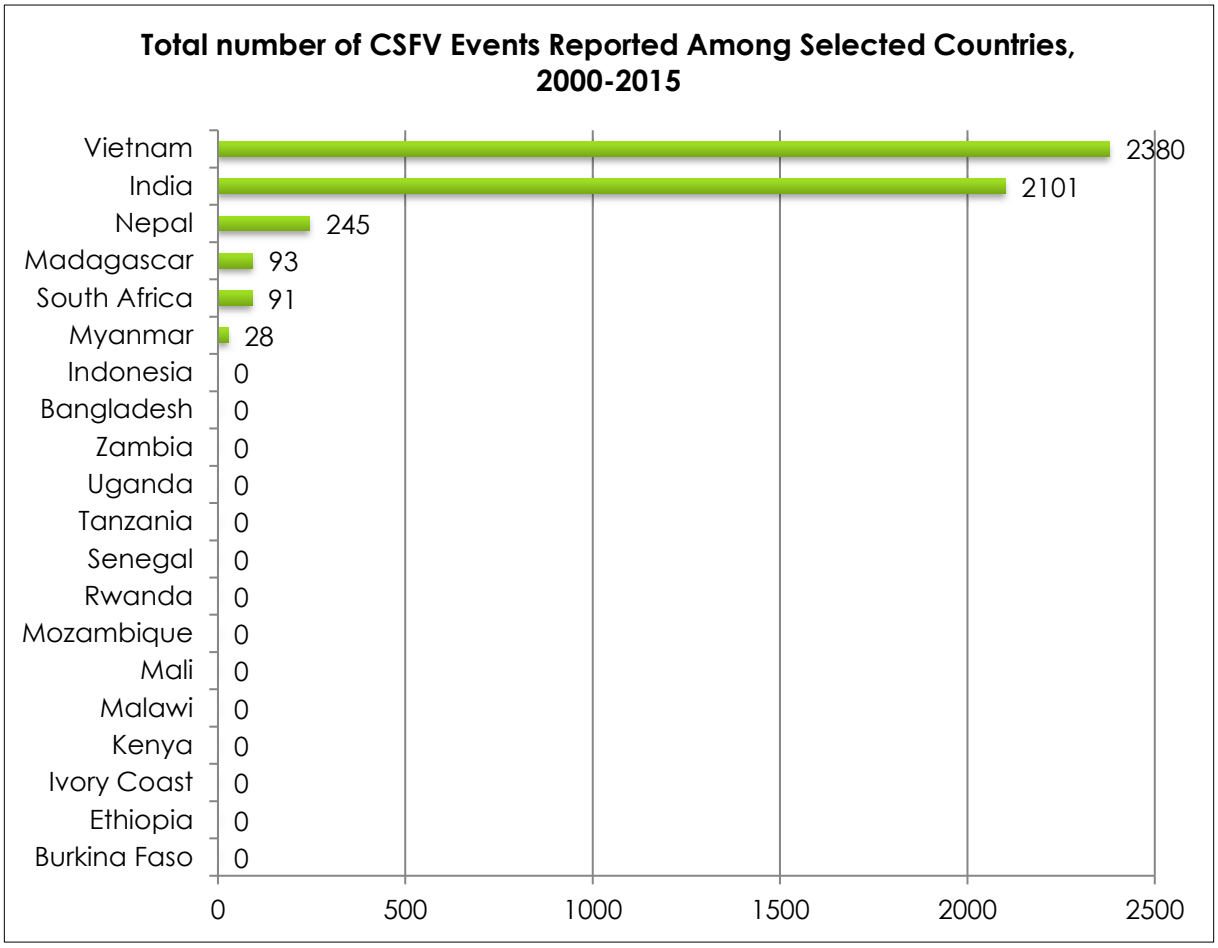


Figure 11: Total number of CSFV Events Reported Among Selected Countries, 2000-2015

The maximum number of 748 CSFV events was reported in 2008 among the 20 selected countries, 2000-2015. Figure 12 presents a graph of the temporal distribution of CSFV events in the 20 selected countries from 2000 to 2015. Among SE Asian countries, incidence of CSF is considered to be higher in Indonesia (despite under-reporting), Vietnam and the Philippines and much lesser in Singapore, Thailand and Myanmar [7].

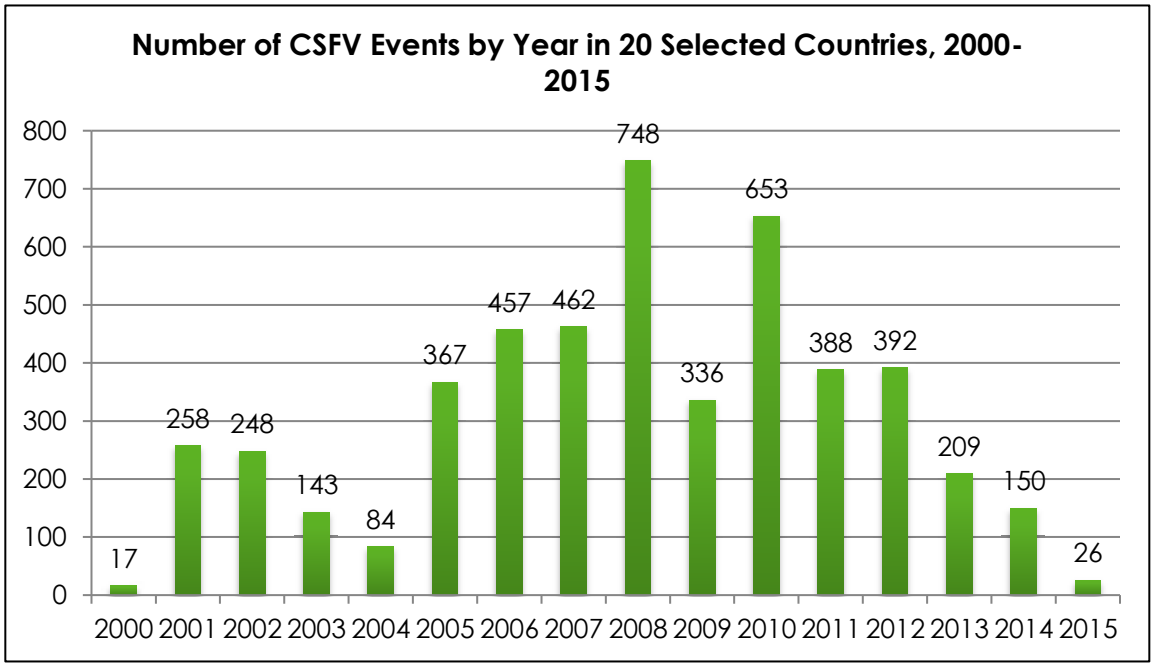


Figure 12: Temporal distribution of CSFV events in the 20 selected countries from 2000 to 2015

In Lao PDR, considerable research on CSFV has been conducted with support from the Australian Animal Health Laboratory (AAHL), Geelong. In 1998, a laboratory project received 257 samples. Fifty were CSFV antigen positive representing 35 outbreaks (I9.5 %of the total samples submitted). In 1999, 87 samples were received with 19 positive samples from 11 outbreaks (21.8 %) [35]. Other additional detailed prevalence estimates at the provincial level in Lao PDR are summarized in Figure 13 [36].

Province of Lao PDR	Type of Pig	Number of Samples Tested Positive (%)	Reference
Oudomxay	Domestic	55 (11.0%)	Khounsy and Conlon, 2008
Prabang		91 (13.0%)	
Phongsaly		88 (15.0%)	
Xayabouly		84 (15.0%)	
Houaphan		161 (6.0%)	

Figure 13: Temporal distribution of CSFV events in the 20 selected countries from 2000 to 2015

Economic and Social Impacts at Global and Regional Levels, and in Selected Countries

Losses of animals of different species are calculated as Livestock Unit (LSU) losses, using the definitions presented in Figure 14 [37].

1 camel or "other camelid"	=	1.1 LSU
1 cattle	=	0.9 LSU
1 buffalo	=	0.9 LSU
1 horse or mule (equidae)	=	0.8 LSU
1 pig	=	0.25 LSU
1 sheep	=	0.1 LSU
1 goat	=	0.1 LSU
1 poultry bird (chicken, duck, guinea fowl or goose).	=	0.015 LSU

Figure 14:

Classical swine fever ranks as the most economically significant disease of pigs globally. An epidemic of CSF, which occurred in the Netherlands in 1997-98, led to the death or slaughter of approximately 12 million pigs as part of the eradication campaign. The cost of this outbreak was estimated to be US$2.5-3 billion [36]. Some general economic impacts of CSF with references are summarized in Table 14.

Table 14: General economic impacts published for CSF disease

Economic Impact of CSF	Reference
The largest direct economic impact of CSF is through reduced production; Morbidity and mortality directly impact upon the farmers' financial viability and can also influence the market price of pork	Rendleman and Spinelli, 1999
Impact depends upon the response strategies adopted by farmers and any possible market effects. The impact can be mitigated if the farmers' income source is diversified or if there are other opportunities to generate income	Le Gall, 2006
National pig restructuring plan in the Netherlands resulted in a reduction of the national pig herd by approximately 25% within two years	FAO, 2002
Bans on the export of products and subsequently may impact upon the market price of pigs	Bech-Nielsen et al., 1993
Of three control strategies in free areas (detecting and stamping-out affected herds; strategies not based on vaccination; and emergency vaccination), not adopting vaccination can minimize the costs for controlling the disease	Saatkamp *et al*. 2000
In extensive pig-holding systems in developing countries the animal and economic losses may be less obvious.	CABI, 2015

CSF accounts for the highest pig losses measured in livestock units lost globally. Figure 15 presents a summary of the ranking of pig diseases in terms of Livestock Units (LSU) lost, 2006-2009 [37].

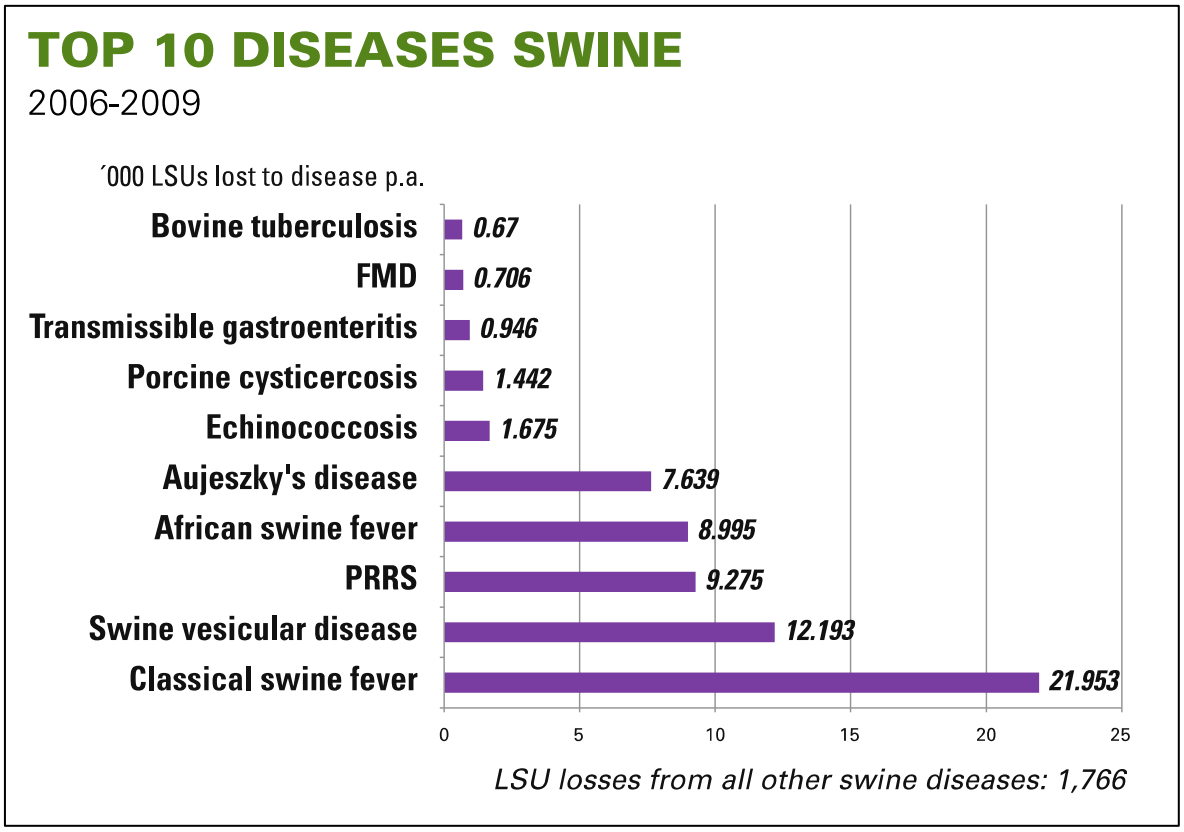
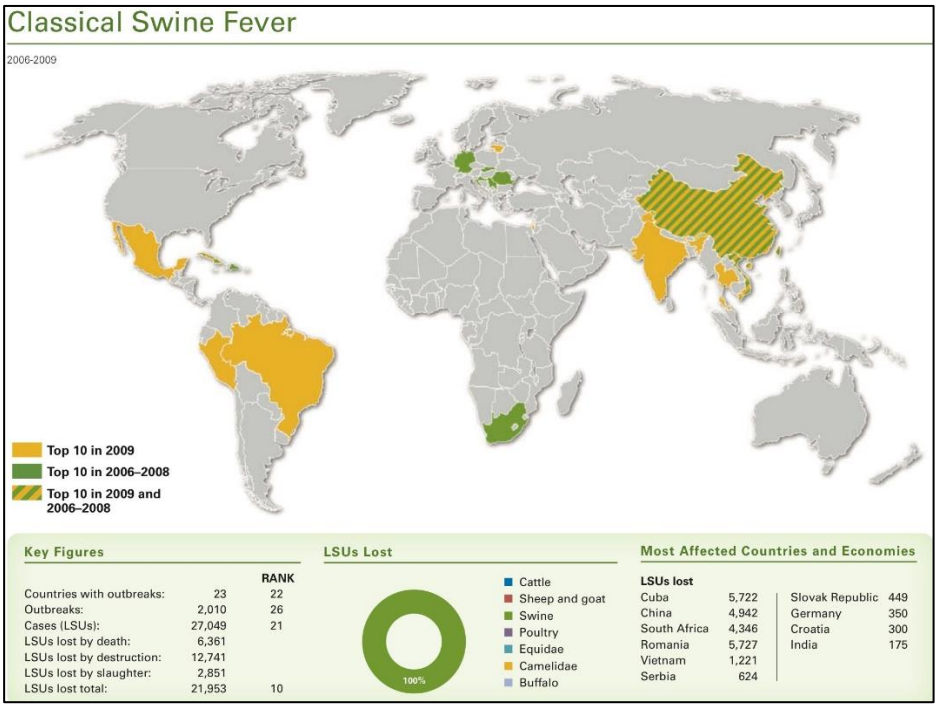


Figure 15:

Figure 16 further summarizes the geographic distribution of the top 10 countries impacted through LSU losses due to CSFV, 2006-2009. In descending order South Africa, Viet Nam and India rank among the most affected among the selected countries [37].

Asia is the largest producer of pork in the world accounting for 56% of global pork production (109,216 thousand tones), with China accounting for 48% of the global pork production [38]. The countries within the ASEAN have a combined 68 million pigs or 7% of the global total of 968.16 million based on 2010-2013 and 2011 estimates, respectively [19]. Table 15 summarizes the population size, production system and trade value for eight ASEAN countries including Indonesia and Viet Nam.

Similar details are not available for the member countries of the SAARC, however the International Livestock Research Institute (ILRI) has projected the economic impact of CSFV in Northeast States of India, presented in Table 16 (**http://asia.ilri.org/2014/02/04/csf-india/**).



a)

b)

Figure 16: Geographic distribution of the top 10 countries impacted through lost LSU due to CSFV, 2006-2009 with b): expanded view of Asian distribution

Table 15: Profile of the pig populations of eight ASEAN countries, production systems and trade values

Country	Population/Year	Type of Operation	Trade/Value
Vietnam	27.4 M/ 2010	70% backyard	domestic/US$60 M
Philippines	11.98 M/ 2014 July	commercial 31%, 69 %backyard	domestic/US$3.66 B
Thailand	9.51 M/ 2013	commercial intensive, 8% backyard	export/US$140.88 M
Indonesia	8.25M/ 2013	small, medium, commercial scales	Export/US$$10.34 M
Malaysia	1.39M/ 2013	large scale	US$479.00 M
Myanmar	4.49 M/ 2012	75% backyard	domestic
Lao PDR	2.46 M/ 2008	70% backyard	domestic
Cambodia	2.4M/ 2013	small scale, subsistence	domestic

Joint FAO/OIE Workshop on Swine Disease Control in Asia

Table 16: Profile of the pig populations of eight ASEAN countries, production systems and trade values

	Assam	Mizoram	Nagaland	Total
Cost of mortality (US$)	30 million	0.51 million	4.04 million	34.55 million
Cost of treatment (US$)	0.364 million	6,646	60	0.371 million
Cost of replacement (US$)	1.542 million	29,152	0.271 million	1.842 million
Total costs (US$)	28.715 million	0.549 million	4.366 million	33.63 million
TOTAL US$				**70.393 million**

Table 17 summarizes the data related to the socioeconomic impacts of CSFV in the 20 selected countries under the LVIF.

Table 17: Socioeconomic impacts of CSFV based on peer-reviewed publications in 20 selected countries

Region/Country	Economic Impact	Social Impact	Year	Reference
Sub Saharan Africa				
Burkina Faso				
Ethiopia				
Ivory Coast				
Kenya				
Madagascar				
Malawi				
Mali				
Mozambique				
Rwanda				
Senegal				
South Africa	The outbreak of CSF in the Eastern Cape, 2004-2007 was the largest pig disease outbreak that South Africa had ever experienced. The socio-economic effects of		2004-2007	Mather, 2010

	the outbreak in the Eastern Cape are informally reported to have been devastating).			
	The South African government paid more than US$13.1 million (R200 million) to compensate the more than 83 000 affected farmers; the compensation paid per pig was US$130; The culling of pigs affected pork availability, income generation and caused ecosystem disturbance in the crop-livestock communal production systems.	22% of the farmers were resisting culling insisting that they were an important part of their livelihoods. Most people (92%) mentioned that they were infuriated seeing government officials going around killing pigs; government's delays in compensating farmers may further explain the hiding of pigs by some farmers. According to the Department of Agriculture (2006);	2007	(National African Farmers Union (NAFU), 2007).
Tanzania				
Uganda				
Zambia				
South Asia				
Bangladesh				
India	CSF incurs direct costs to farmers, mainly as stock morbidity, cash treatment costs, and replacement cost of dead animals and overall loss of livelihood. Veterinary authorities incur costs associated with preventing the disease		2014	ILRI, 2014

	and managing outbreaks, while national economies are impacted through restrictions on trade opportunities.			
	Pig farmers in India incur huge losses from mortality, treatment and replacement costs—over US$30.3 million each year		2012	ILRI, 2012
Nepal				
Southeast Asia				
Indonesia	300,000 to 400,000 pig mortalities from a total population of approximately one million pigs were reported in Bali alone		1995	Bulu, 2011
Myanmar	Risk of CSFV from neighboring Indian State of Mizoram		2014	ILRI, 2914
	Mizoram bans import of pigs from Myanmar		2013	Business Standard, http://www.business-standard.com/article/pti-stories/mizoram-bans-pig-import-from-myanmar-113042100305_1.html, 2013

Vietnam	Classical Swine Fever (CSF) and Newcastle disease (ND) are endemic and serious threats to small-scale producers, while FMD is a major threat to the emerging intensive dairy sector. Overall, CSF and ND are probably of greater economic relevance than FMD, although the latter has most attention; Foot and Mouth Disease and Classical Swine Fever are more important barriers to global market access, in particular to the main OECD countries markets.		2006	Vietnam Food Safety and Agricultural Health Action Plan, 2006
	Losses per pig due to CSF range from US$23 to US$ 28 in Viet Nam; at the household level, this amounts to between US$53 and US$295; the highest losses in households that raise and fatten pigs (multi-age holdings)		2000	Lai Thiu Kim Lan, 2000 [39]

Disease Prevention and Control Methods

Treatment (Control)

Sanitary Measures

Sanitary measures for the Control of CSF during outbreaks, with particular emphasis on the smallholder pig production system are listed below [4][19][40][41][42][43]:

- Policy for culling if feasible;
- Slaughter of all pigs on affected farms;
- Safe disposal of carcasses, bedding, manure and contaminated waste;
- Thorough cleaning and disinfection;
- Designation of infected zone, with inter-jurisdictional control of pig movements;
- Detailed epidemiological investigation, with both up-stream tracing of possible sources and down-stream tracing for possible spread of infection;
- Surveillance of infected zone, and surrounding area;
- EU measures in the case of a CSF outbreak: depopulation of infected herds, surveillance and movement restriction in the 3 and 10 km zones and surveillance in herds that have been in contact with infected herds plus depopulation of contact herds [40];
- In a region with a low farm density, the basic EU measures are sufficient to control an epidemic. In a region with a high farm density, depopulation of contact herds would not be necessary [41].
- Reducing the number of animal movements significantly reduces the size and length of epidemics in areas with high pig density [42].
- Early detection of CSFV is critical. A recent experimental study demonstrated that the nictitating membrane (third eyelid) provides a useful source of virus in pigs which have undergone autolysis, since it is much less affected by autolysis than the internal organs [34];
- Emergency vaccination in addition to eradication can reduce control costs provided that the vaccinated animals can be sold for commercial slaughter and not culled [42];

- The modified live vaccine for CSF would be the vaccine of choice, since immunity develops rapidly [43]. Although preferable, the use of a marker vaccine is not essential for emergency vaccination, provided vaccinated animals are clearly identified by some other means such as ear tags or tattoos [42].

Medical Measures

No medical treatment exists for CSFV and so virus source reduction through effective and humane culling and carcass disposal are the main ways to reduce environmental load and further transmission.

Prophylaxis (Prevention)

Sanitary Measures

The following sanitary prophylactic measures have been recommended [4][44]:

- Education, awareness raising and on going communication between veterinary authorities, veterinary practitioners, traders and pig farmers;
- Effective disease reporting system;
- Strict import policy for live pigs, pig semen, and fresh and cured pig meat;
- Quarantine of new pigs being admitted into the herd;
- Efficient cooking or prohibition of waste food fed to pigs;
- Effective biosecurity plan for rendering plants, personnel;
- Structured serological surveillance targeted to breeding sows and boars;
- Effective pig identification and recording system for tracing;
- Effective hygiene measures protecting domestic pigs from contact with wild boar and feral pigs;
- Zoning and compartmentalization based on formal risk assessments [44].

Medical Measures

The following medical prevention measures should be contextually relevant and based on OIE recommendations and peer-reviewed studies [4][39][43]:

- Enzootic countries: Vaccination with modified live virus strains is effective in minimizing losses but it cannot eliminate infection;
- Countries free of CSF, or in the process of eradicating CSFV: Culling and eradication is practiced while vaccination is normally prohibited [4][39];

- In the highly endemic areas in Southeast Asia: Routine vaccination against CSF is the most common means used for prevention and control. However, the increased incidence of chronic CSF during the 1990s in some countries has raised concerns as to whether the vaccines and the vaccination programs have been effective [43]. An intensive and systematic CSF vaccination program in the backyard production system in Viet Nam was predicted to be beneficial [39].

The Situation in Southeast Asia

The official Disease Control programs of CSF for Indonesia, Myanmar and Viet Nam specified under national and ASEAN regional frameworks are summarized in Table 18 [19].

The Situation in South Asia

India has adopted a Classical Swine Fever Control Programme included in the existing Scheme of Livestock Health and Disease Control. An amount of US$4.7 million has been allocated for the Livestock Health and Disease Control Programme for the Twelfth, Five-Year Plan. The 'Classical Swine Fever Control Programme (CSF-CP)' has been added in the existing scheme of LH&DC during 2014-15. Funds on 100% central share basis are provided to the States/Territories for carrying out the vaccination of entire eligible pig population in a phased manner starting in the Northeastern States. Depending on the vaccine availability, the scope will be enlarged to cover entire country subsequently [46].

As noted, vaccination for CSF is practiced in India, but not to any significant extent in Nepal or Bangladesh. Swine is not a prioritized animal species in Bangladesh and is being reared mostly by the lower caste Hindu communities mainly hilly area, south and southwestern part of the country. The pigs in this country are the indigenous (native) type and husbandry practices are mainly the free reaming roaming or scavenging system. Each community includes holdings with only a few pigs that freely roam within the village. As pigs are neglected and number less than one million), no vaccine has been introduced and the Department of Livestock Services has no plan to vaccinate the swine population.

Table 18: Official national and regional control measures adopted by Indonesia, Myanmar and Viet Nam

Control Measures	Indonesia	Myanmar	Viet Nam
Regional Classical Swine Fever (CSF) Control and Eradication Plan	✓	✓	✓
National Classical Swine Fever (CSF) Control and Eradication	✓	-	✓
Regulatory Measures	-	-	-
Disease Surveillance	✓	-	✓
Laboratory Diagnosis	✓	✓	✓
Epidemiological Analysis	✓	✓	✓
Vaccination	Mandatory	-	-
Animal Movement Management	✓	✓	✓
Legislation/Policy	✓	✓	✓
Research and Development	✓		
Zoning/ Compartmentalization*	✓	-	✓
Socio-Economics (compensation, budget)	-	-	-
Public Awareness	-	-	-

Options and Strategies for Vaccination

The most common CSFV vaccine strain is the Chinese C strain. The GPE– strain, the Thiverval strain, and the Mexican PAV strains are also regionally used [47]. The subunit marker vaccines based on the E2 protein are produced but are not used for smallholder pig units in ASEAN or SAARC countries. All strains previously noted have DIVA capability except for the Chinese C strain. The advantages and disadvantages for each strain are presented in Table 19.

Table 19: Advantages and disadvantages of CSFV vaccine models

Vaccine Strains	Advantages	Disadvantages
C Strain (rabbit tissue culture)	• No clinical signs or replication of the challenge virus 4 days post vaccination • Protection is longer than one year and most likely provides lifelong immunity • Can block transmission of the challenge virus from at least seven days post vaccination • Does not interfere with gestation, nor is it harmful to the fetuses, and in immunosuppressed sows • Effective and reasonable cost	• Maternal antibodies interfere with the induction of vaccinal immunity • Lacks DIVA capability
C Strain (cell culture line)	• Similar to C strain tissue origin in safety and efficacy • Mass production techniques can be applied to increase the amount of vaccine available to meet demand • Effective and reasonable cost	• Many products lack quality and consistent efficacy • Maternal antibodies interfere with the induction of vaccinal immunity • Lacks DIVA capability
GPE Strain (cell culture)	• DIVA capability - expression of different *in vitro* markers, e.g. interference with the growth of Newcastle disease virus in swine testicle cell culture • Safety and efficacy similar to C strain • Rarely produces viraemia in inoculated swine and is not shed in excretions. • Protection observed beginning at about three days post vaccination	• Maternal antibodies interfere with the induction of vaccinal immunity

	• Widely used in Asia	
Thiverval (cell culture)	• DIVA capability - expression of different *in vitro* markers • Safe and effective protection	• Maternal antibodies interfere with the induction of vaccinal immunity
PAV (cell culture)	• Regionally specific application in Mexico	• Maternal antibodies interfere with the induction of vaccinal immunity • Efficacy of the vaccine differed markedly in field conditions compared to under laboratory conditions
E2 subunit marker vaccine (E2 glycoprotein expressed in a baculovirus vector)	• DIVA capability - expression of different *in vitro* markers • Highly safe with no side effects were observed in swine following administration of the vaccine • Slight tissue reaction at injection site	• Slow onset of immunity - protection of piglets against the clinical course of CSF two weeks after double vaccination or six weeks after single vaccination with the E2 subunit vaccine • Experiments assessing horizontal and vertical transmission of challenge virus gave varying results

Well-informed strategies for the selection and implementation of effective CSFV vaccines should be based on antigenic, immunologic and epidemiologic information. Suradhat et al. and other researchers have provided reviews, which serve to support planning and decision making related to vaccination strategies for CSF. Table 20 presents a summary of relevant evidence and options to support the most effective strategies for vaccination for CSFV [3][34][43].

Table 20: Evidence and options to support effective vaccination strategies for CSFV

Evidence	Options	Reference
There has been a decline in the number of peracute outbreaks due to Genotype 1 and an increased incidence of subacute and chronic CSF outbreaks caused by the moderately virulent CSFV, genogroup 2.2.	The C strain, modified live vaccine (MLV) has been regarded as one of the most effective CSF vaccines that provides complete clinical and virological protection, i.e. sterile immunity, within a week of vaccination; it is well accepted that CSF-MLV can effectively induce complete protection against all of the CSFV strains	Suradhat et al., 2001; Van Oirschot, 2003
Pigs vaccinated with the C-strain vaccine appear to be completely protected against virulent CSFV challenge as early as 1 week following vaccination	When vaccinated pigs were challenged at a later stage after vaccination, there was a good correlation between the presence of neutralizing antibodies at the time of challenge and viral protection	Terpstra and Wensvoort, 1988; Suradhat et al., 2001; Van Oirschot, 2003
The C strain vaccine usually induces detectable neutralizing antibodies in vaccinated pigs 2–3 weeks following primary vaccination	Routine monitoring of SN titers, i.e. seroprofile, can still be used for assessing the effectiveness of a CSF vaccine program in the field. There is a strong recommendation for routine monitoring of herd immunity to CSFV, in farms situated in highly endemic areas. The C strain CSF-MLV is the vaccine of choice for an emergency vaccination protocol	Precausta et al., 1983; Terpstra et al., 1990; Van Oirschot, 2003; Graham et al., 2012
A single vaccination of the CSF-MLV, including C strain (both lapinized and tissue culture derived) and GPE- strains, induced complete protection against CSFV infection as early as 6 days after vaccination. It should be noted that this protective effect was observed on the condition that the pigs had low levels of MDA at the time of vaccination	The C strain, modified live vaccine (MLV) has been regarded as one of the most effective CSF vaccines that provides complete clinical and virological protection, i.e. sterile immunity, within a week of vaccination	Suradhat et al., 2001; Suradhat and Damrongwatanapokin, 2003
Combining the C-strain vaccine and a live gE-deleted, PRV vaccine resulted in a significant reduction in cellular response against CSFV, while there were no	Vaccination of the CSF vaccine combined in the same injection with other vaccines	Suradhat et al., 2001

differences in the levels of SN antibody. Although the pigs vaccinated with the combined vaccine were clinically protected against CSFV challenge, there were clearly more fever days and pathological changes in this group, when compared to those from the pigs vaccinated with the CSF vaccine alone	should be systemically tested prior to implementation.	
E2 subunit vaccine, which mainly activated the CSFV-specific T helper cell population and the production of neutralizing antibodies, confer clinical protection against the CSFV challenge	Protective values of the E2 subunit vaccines are inconsistent; vital role of cell-mediated immunity for controlling viral spreading in the challenged animals.	de Smit et al., 2001; Uttenthal et al., 2001; Dewulf et al., 2002; Van Oirschot, 2003
Oral CSF-MLV vaccination was introduced by the European countries for the purpose of controlling CSF in wild boars. To obtain complete protection, the oral CSF vaccine formulation requires the addition of a vaccine stabilizer and a higher dose of the MLV virus	Vaccine protocols using a commercially available CSF vaccine for oral immunization of domestic pigs are not recommended at the moment.	Van Oirschot, 2003; Kaden et al., 2000).
Piglets immunized at 5 weeks old developed a greater number of CSFV-specific, IFN-g producing cells in the PBMC and higher CSFV-specific, SN titers than pigs immunized at 3 weeks old	Interference by maternal derived antibodies (MDA) is the most common factor affecting the induction of protective immunity against CSFV in the field.	Suradhat and Damrong-watanapokin, 2002
PRRSV infection significantly interfered with induction of CSFV-specific immunity which resulted in vaccine failure	This finding implied that CSF vaccination during the active stage of PRRSV infection should be avoided. Taken together, the above findings emphasize that the influence of other pathogens on the immune system and/or interactions among the pathogens should also be taken into consideration. Strict biosecurity and routine monitoring of the herd immune status will be crucial for preventing such complications.	Suradhat et al., 2006
CSF vaccine failure that is observed in the field is primarily due to a lack of understanding of the herd immune status,	Sharing such information among veterinary researchers, swine practitioners and farmers, together with a strengthening of	[43]

mechanisms of immunological protection, viral pathogenesis, and epidemiology	the disease surveillance program is necessary for a successful CSF preventive and control program	
Vaccination in a ring of 2 km radius around a detected infection source is as effective as ring culling in a 1 km radius. Feasible screening scenarios, adapted to the use of emergency vaccination, can reduce the enhanced risks of (initially) undetected farm outbreaks by targeting vaccinated farms.	Results suggest that emergency vaccination against CSF can be equally effective and safe as pre-emptive culling in a densely populated region	Backer et al., 2009
Although MLV provide earlier and more complete protection than E2 subunit vaccines, it has the drawback of not allowing DIVA. The marker vaccine of E2 protein with companion discriminatory test to detect antibodies against E^{rns} allows DIVA and is a promising strategy for future control and eradication of CSF.	Maternal derived antibody (MDA) is the critical factor in impairing the efficacy of both MLV and E2 subunit vaccines, so the well-designed vaccination programs of sows and piglets should be considered together; it is necessary to evaluate whether the E2 subunit vaccine can completely protect against the current prevalent strains in the field; ideally a new generation of vaccine should be able to maintain the high protective efficiency of MLV and overcome the problem of antigenic variations while allowing for DIVA	Huang et al., 2014; Rijn et al., 1997
The subunit vaccines were found to be less efficacious than live attenuated vaccines. In addition, the currently available discriminatory tests do not provide high enough specificity and sensitivity; there is an urgent need for more advanced marker vaccines and better discriminatory tests	Development of new DIVA vaccines against CSF is hampered by the small market potential for these products	Greiser-Wilke and Moennig, 2004
Although marker vaccines can limit the speed and the extent of virus dissemination and thus reduce the number of animals slaughtered	Marker vaccines are no substitute for sanitary measures. Early detection and warning systems and the quick implementation of sanitary measures, including stamping out, remain key issues in the control of highly contagious diseases.	Vannier et al., 2007

The virulence, immunogenicity, and ''marker vaccine'' properties of the generated chimeric CP7_E2alf virus were determined in an animal experiment using 27 pigs	Chimeric CP7_ E2alf may not only serve as a tool for a better understanding of Pestivirus attachment, entry, and assembly, but also represents an innocuous and efficacious modified live CSFV ''marker vaccine''	Reimann et a., 2004; Tognon et al., 2010
Glycoprotein E^{rns} of classical swine fever virus (CSFV) was used to rescue CSFV Erns deletion mutants based on the infectious copy of CSFV strain C. The biochemical properties of E^{rns} from this cell line were indistinguishable from those of CSFV Erns	Absence of the antigenic part of E^{rns} in the recombinant viral particles can be used to differentiate between infected and vaccinated animals	Widjojoatmodjo et al., 2000
CSFV vaccine C-strain and group 2 strains circulating in China differ in the antigenicity of their E2 glycoproteins.	Need to conduct serological differential assays and improvement of immunogenicity of novel classical swine fever vaccines; There is a clear need for efficient and safer marker vaccines to assist in the control of future CSF outbreaks.	Chen et al., 2010; Ganges et al., 2008
First report demonstrating the absence of a response to vaccination in CSFV persistently infected pigs	Herd virus and serological monitoring of all age groups is needed to avoid vaccine failure	Muñoz-González et al., 2015
PRV (Aujesky's disease) mutant was used as a biologically safe vaccine vector, a gD/gE-negative PRV recombinant virus, which expresses envelope glycoprotein E2 of classical swine fever virus was constructed.	Vaccination of pigs showed that the recombinant virus was able to protect pigs against both Aujeszky's disease and classical swine fever.	Peeters et al., 1997
Subunit vaccines, conventional, live attenuated CSF vaccines have a rapid onset of immunity and are effective at preventing transmission of infection, but have the disadvantage that it is not possible using serological methods (e.g. ELISA) to differentiate infected pigs from those that have merely been vaccinated; commercial E2 subunit vaccines (Marker vaccine) have a slower onset of immunity	These vaccines enable a DIVA strategy to be followed thereby facilitating a 'vaccination to live' strategy; the vaccine only elicits antibodies against the E2 glycoprotein and therefore antibodies against other CSFV antigens, such as the E^{RNS} antigen, can be used as markers of infection.	Van Oirschot, 2003; [3];

and reduce, but may not completely prevent, viral shedding and transplacental infection		
The main stumbling block to using vaccination as a control measure is the potential impact on trade; the main disadvantage of the E2 marker vaccine was that protection was only complete 3 weeks after vaccination, which would diminish its usefulness as an emergency vaccine	Subunit marker (DIVA) vaccines against CSF with a companion diagnostic test to trace residual infections by detecting antibodies not induced by the vaccine have been developed; more efficacious DIVA technology are ongoing, because the immune response is delayed and less protective than that to the live attenuated vaccines Research is also directed towards improving the tests used to distinguish naturally infected and vaccinated animals	[34]; Moormann et al., 2000; Beer et al., 2007; Zhao et al., 2008

From the evidence presented above, a strategy for CSFV vaccination should consider the following elements:

- Establish appropriate enabling mechanisms
    - Enabling mechanisms including national policies for pig production, animal identification, official control or eradication policy and vaccination;
    - Prioritization of important pig disease priorities (e.g. PRV) regulations and contingency plans for CSF, including provisions for zoning and compartmentalization;
    - Laboratory and epidemiological capacity to implement seromonitoring and virus surveillance programs;
    - On going communication and information sharing among public, private sectors to raise awareness and mobilize local communities to develop and monitor program progress and effectiveness;
    - Conduct risk assessments and cost-benefit studies to evaluate the proper use of culling and vaccination;
- Evaluate the presence of all immunosuppressive disease agents such as PRRS routinely as a normal component of assessing risk and designing the vaccine program including seromonitoring. This will be critical to address in Viet Nam, Indonesia, Myanmar and India where PRRS has significant health, social and economic impacts.
- Conduct risk assessments and develop effective vaccine planning and delivery systems from national to the local level to meet national objectives within the OIE standards;

- Utilize the appropriate type of vaccines under each of the following epidemiological contexts:
    - Free areas of CSFV with Trade Access: Develop a control strategy without prophylactic vaccination but establish legal provisions for emergency vaccination scenarios [34];
    - Endemic Areas: Modified live 'C' type vaccine routine use in endemic areas with rapid onset of cell mediated immunity within 6 days [43]; or alternatively, use of E2 subunit vaccines [34];
    - Emergency Scenarios: Rapid diagnosis is crucial for the control of outbreaks. The combined use of culling and emergency vaccination during epidemic incidents in areas with high density pig populations can be further considered to control and eradicate the disease [40][42];
    - Progressive elimination and freedom from CSFV: E2 subunit marker vaccines can used to DIVA along with zoning and compartmentalization approaches for the final removal of the need for vaccination [3].

Table 21 presents the official prevention and control policies from a survey of the 20 selected countries under the LVIF for classical swine fever.

Table 21: Official prevention and control policies for CSF among the 20 selected countries.

Classical Swine Fever (CSF)	Notifiable	Official surveillance program	Official control program	Vaccination				Treatment/Chemotherapy	
	(yes/no)	(yes/no)	(yes/no)						
Country				Compulsory vaccination	Who pays for the vaccine?	Who delivers the vaccine?	Species vaccinated	Treatment authorised	Frequently practiced
				(yes/no)	(Government, farmers, combination, others- specify)	(official, private vaccinators or both)	(cattle, sheep, goats, pigs, poultry)	(yes/no)	(yes/no)
Burkina Faso									
Ethiopia									
Ivory Coast	OUI	PASSIF MAIS ACTIF EN CAS D'EPIZOOTIE	OUI	NON				NON	
Kenya	no	Yes, passive	no	NA	NA	NA	NA	NA	NA
Madagascar									
Malawi	YES	YES(PASSIVE)	NO	N/A	N/A	N/A	N/A	N/A	N/A

Mali									
Mozambique									
Rwanda									
Senegal									
South Africa									
Tanzania									
Uganda	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Zambia	Yes	Yes - passive	Yes	N/A	N/A	N/A	N/A	No	No
Bangladesh	Yes	No	No	No	No	No	No	No	No
India									
Nepal	Yes	yes/passive	No	No	combination	both	Pigs	N/A	N/A
Indonesia									
Myanmar	yes	yes(passive)	no	no	Farmers	Both	pig	no	yes
Vietnam	Yes	Yes/Passive	No	Yes	Farmers	Private vaccinators	Pigs	No	Yes

[1]Surveillance: is the systematic on going collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken.

[2]Control: a programme which is approved, and managed or supervised by the Veterinary Authority of a country for the purpose of controlling a vector, pathogen or disease by specific measures applied throughout that country, or within a zone or compartment of that country.

Vaccines Available

South Asia, less than 2% pigs are vaccinated against CSF, mainly due to the lack of availability of vaccine and poor awareness among smallholders. In Southeast Asia, 50-90% of pigs (the nearer to the town, the higher the percentage) are vaccinated against CSF [45]. Besides vaccination, there are policies for movement control of diseased animal and slaughter of diseased pigs in certain countries including Thailand, Vietnam, and Malaysia [7].

Commercial vaccines manufactured in Africa and Asia

Table 22: Commercial CSF vaccines manufactured in Africa and Asia [48][49]

Specific Vaccines and Formulation	Strengths	Weaknesses	Opportunities	Threats
Live Attenuated (modified live)				
BSL-HC Bestar Laboratories Pte. Ltd. China, Singapore	GPE strain is a marker vaccine compatible with DIVA using CHEKIT diagnostic and differentiating test kits;	Requires countries to have proper test kits	Widely used in Asia; DIVA capacity during late stages of eradication	Laboratory and resource sustainability
Coglapest, 2 ml intramuscular; Ceva Sante Animale (Philippines, Bangladesh,	Thiverval strain with rapid onset of immunity could be given as early as 5 days of age; twice annual vaccination; vaccinate 3-6 weeks before farrowing	Do not use during gestation; Short duration of immunity – 4 months; must be given at 35 days of age and then boost 3-4 weeks later; 50	Widely used in Asia; From 1 single shot (from 35 days of age) in low risk conditions (non-endemic situation, isolated farms) to a 2 shots programme (1st shot from 3 to 4 weeks of	None

Indonesia, Vietnam)		dose vials; keep refrigerated 2-8℃	age, completed with a 2nd shot 3 weeks later) in high-risk conditions(CSF endemic situation, poor biosecurity).	
Pestiffa, Merial (France, Philippines, Russian Federation)	Protects against clinical disease and from becoming a carrier-shedder for older pigs and congenitally infected piglets; China CL strain lapinized tissue derived with 24 months of long term protection; 10, 20 and 50 dose vials; safe and effective; safe in pregnant sows	Lacks DIVA capability	Widely accepted and used due to safety and efficacy	Lacks DIVA capacity in late stages of virus eradication
Porcilis CSF Live, GPE- MSD Animal Health (Phlippines)	DIVA capability; moderately longer duration of immunity Fattening pigs: single dose at 1-2 months of age, depending on the level of maternally derived antibodies (MDA). Breeding pigs: vaccinate at 1-2 months of age, depending on MDA. Revaccinate 6 months later and then once a year; smaller dose of 1 ml intramuscular	Must have laboratory test kits and capacity; 50 dose vials; store at 2-8℃	DIVA in late stages of eradication	Laboratory and resource sustainability
Ramjivax, GPE strain; I ml intramuscular, Institut Malgache des Vaccins	DIVA capability; Vaccinate at 6 weeks and then annually; 10 dose vials available; immunity develops	Not safe for use during gestation; keep refrigerated	Potential access to African markets; DIVA in late stages of eradication	Acceptability by farmers of safety concerns during gestation

Veterinaires (IMVAVET) (Madagascar)	after 5 days; protection for European strains of CSF; 12 months duration of immunity			
Swine Fever Thermo-Stable Live Vaccine; Intramuscular or subcutaneous; Chengdu Tecbond biological products (China)	Thermostable C strain attenuated HCV virus liquid and some heat resistant protective agent; Protection begins 4 days following vaccination with duration of 12 months; piglets should be vaccinated twice at 21-30 days old and around 65 days old respectively; replacement gilts should be vaccinated twice before breeding and the interval of the two vaccinations is 3 weeks.	Store at 2-8℃	Stable once the vaccine is reconstituted	Vaccine must be stored under refrigeration
Classical Swine Fever Vaccine, Live (Tissue Culture Origin); CSFV lapinized strain (CVCC AV1412); intramuscular or subcutaneous; Weke Biotechnology (China)	C Strain with rapid onset of immunity; injected pigs will get immunity after 4 days of injection. For the Piglets without maternal antibody after weaning, the immune period lasts for 12 mouths; piglets without maternal antibody after weaning can be vaccinated just once. Otherwise, the piglets should be vaccinated twice at 21-30 days old and	Requires storage temperature at minus 15℃ without sunshine	Potential market access in Asia	Lacks DIVA capacity in late stages of virus eradication

	around 65 days old respectively			
CLASSICAL SWINE FEVER VACCINE, LIVING; PK-15 cell culture line; 1 ml intramuscular; Hester Biosciences Limited (India)	Vaccinate at 6 - 8 weeks and with a booster dose 3 - 4 weeks later Sows and gilts should be vaccinated before mating. Boars should be vaccinated twice a year; 5 dose, 10 dose and 20 dose pack	No claims of safety except no tissue reaction; Store below 8°C	Potential market access in Asia	Uncertainties related to K-15 cell line
Classical Swine Fever Vaccine; CSFV lapinized strain of rabbit spleen tissue virus (CVCC AV1412); intramuscular or subcutaneous; Qilu Animal Health Products Factory (China)	C Strain; Prevention of Classical Swine Fever. The injected pigs will get immunity after 4 days of injection. For the Piglets without maternal antibody after weaning, the immune period lasts for 18 months	Preserved at a temperature at minus 15℃. The vaccine will be efficacious for only 12 months.	Potential market access in Asia	Lacks DIVA capacity in late stages of virus eradication
Swine Fever Thermo-stable Vaccine, Live (Rabbit Origin); 1 ml intramuscular or subcutaneous; each dose with at least 0.01g swine fever spleen virus (Rabbit Origin); Ringpu (Tianjin) Bio-Pharmacy Co., Ltd. (China)	C Strain; Prevention of swine fever and strong immunity is produced in 4 days after vaccination and last for 18 months for weaned piglets without maternal antibody; Safe: The piglet before weaning can be inoculated with 4 doses of the vaccine, so as to prevent the interference of maternal antibody;	Delivered and stored under 8℃	Potential smallholder market access in Asia	Lacks DIVA capacity in late stages of virus eradication

	stable once reconstituted; 5 doses/vial, 10 doses/vial, 20 doses/vial; 40doses/ vial			
Classical Swine Fever Vaccine, Live (Cell Line Origin); CSFV lapinized strain (CVCC AV1412); 1 ml intramuscular or subcutaneous; Ringpu (Tianjin) Bio-Pharmacy Co., Ltd. (China)	In the regions without the prevalence of CSFV, the Piglets without maternal antibody after weaning can be vaccinated just once; otherwise, the piglets should be vaccinated twice at 21-30 days old and around 65 days old respectively; The vaccine will be efficacious if stored for 18 months.	Keep at a temperature of minus 15℃ without sunshine.	Potential market access in Asia	Lacks DIVA capacity in late stages of virus eradication
E2 subunit marker vaccine				
Porcilis Pesti, Inactivated water in oil adjuvant; 2 ml intramuscular; MSD Animal Health (Phlippines)	DIVA capability; can be used during pregnancy; Primary vaccination course: two doses separated by 4 weeks. Revaccination: every 6 months.	May not prevent transplacental transmission of Classical swine fever field virus from the sow to fetuses; slow onset of immunity; mild transient tissue reaction at injection site.	DIVA in late stages of eradication	Support for laboratory kits required; genetically modified vaccines are not permitted in Indonesia

Table 23: Commercial vaccines imported into the 20 selected countries under the LVIF 2012-2015

Classical Swine Fever (CSF)	Name	Strain or type	Country of origin	Doses imported 2015	Doses imported 2014	Doses imported 2013	Doses imported 2012
Burkina Faso							
Ethiopia							
Ivory Coast							
Kenya							
Madagascar							
Malawi							
Mali							
Mozambique							
Rwanda							
Senegal							
South Africa							
Tanzania							
Uganda	NA	NA	NA	NA	NA	NA	NA

Zambia							
Bangladesh	No	No	No	No	No	No	No
India							
Nepal							
Indonesia							
Myanmar	Pestifer	Chinese Strain	China	112,000	304,000	4,590,000	30,000
Vietnam			• Komipharm International • Choongang Vaccine Laboratory • Daesung Microbiological Lab • Formosa Biomedical • Kaohsiung Biological Product • Vaccines and Pharmaceuticals Sdn. Bhd • Kyoritsu Seiyaku Corporation • Merial • Ceva Sante Animale • Bestar Laboratories • Chengdu Medical E&P of China Animal Husbandry • Guangdong Dahuanong Animal Health Products				

Characteristics of Ideal Vaccine Candidates for Smallholders

The optimal CSF vaccine should have the following general characteristics: short- and long-term safety for target and non-target species (especially for oral vaccines); stability, rapid induction of a stable, preferably life-long immunity; efficacy against all strains and types of field viruses; full clinical protection and protection against carrier states; and prevention of horizontal and vertical transmission. Furthermore, marker vaccines will require reliable discriminatory tests [3]. Blome et al. described several research initiatives undertaken by the European Union funding including: 1) 'Immunological mechanisms of protection against CSFV: towards the development of new efficacious marker vaccines'; and 2) 'Identification of efficacious delivery systems for recombinant and nucleic acid construct vaccines'. The third EU-funded project involves investigation of vaccination strategies in wild boar [47]. A review of the gaps is available and results are included in the following Target Product Profile [51].

Target Product Profile

A target product profile for live attenuated vaccines relevant to smallholder pig production is presented to accommodate the different epidemiological stages inherent for prevention, control and eradication.

Attribute	Minimum (currently available vaccine)	Ideal
Antigen	Lapinized C strain	Cell culture C strain with marker
Indication for use	Prevention of classical swine fever for 1) adult carrier pigs; 2) congenitally infected piglets	Same
Recommended species	Pigs	Same or oral

Recommended dose	1-2 ml	1 ml
Pharmaceutical form	Rabbit tissues (fat or spleen) monovalent	Multivalent capacity with PRV when needed (Aujesky's disease)
Route of administration	Intramuscular, intradermal or subcutaneous	Same
Regimen – primary vaccination	1-8 weeks (7-56 days)	1-5 weeks (7-35 days)
Regimen – booster	3-4 weeks later	3-4 weeks after first vaccination followed by boosters based on specific village herd serological profiles with consideration for co-circulating immunosuppressive diseases e.g. PRRS.
Epidemiological relevance and use for smallholders	Currently useful for prevention and control in endemic or emergency situations; No DIVA capability	Prevention, control and eradication with DIVA capability
Recommended age at first vaccination	35 – 56 days of age	As early as 35 days of age based on herd profiling
Onset of immunity	Cell immune response in 4-6 days post vaccination	Same
Duration of immunity	4-48 months	48 months ideally
Expected efficacy	99-100%	Same
Expected safety	99-100%	Same
Withdrawal period	0	Same
Special requirements for animals	Base e of first vaccine on seromonitoring titers of sows for CSFV and PRRS; safe for use in gestating sows and foetuses	Same
Special requirements for persons	Handle and inject safely to avoid possible tissue reaction or anaphylaxis	Same
Package size	10-50 doses per vial	Same

Price to end user	US$ 0.16-0.20 per dose	US$ 0.16 per dose
Storage condition and shelf-life as packages for sale	Require storage without exposure to ultraviolet light either at: 1) 2-8°C; or 2) -15°C	Thermostable vaccine at ambient temperature in storage and during use
In-use stability	Either use within 3 hours or longer thermostability	Ideally 8 hours

Key Conclusions Related to Vaccination

The following conclusions are presented with respect to vaccination for classical swine fever for smallholder pigs:

- The CSF vaccine selected must be fit for purpose in relation to the epidemiological context of Asian countries;
- A CSF vaccination program should be optimized by including veterinary and farmer education herd related to seromonitoring prior to, during and following a vaccination campaign in order to assess: 1) the chronic form of CSF; 2) the presence of immunosuppressive diseases such as PRRS; as well as 3) the timing of vaccination related to the decay of maternally derived antibodies;
- The CSF 'C' and GPE strains are safe and effective vaccines which cover a broad range of CSFV genotypes and serve an important role in the prevention and control of CSF in Asia and Europe;
    - The need for a marker to expand the DIVA capability for 'C' strain;
    - Further basic research and field testing of GPE marker vaccine including field trials;
    - Transition from the lapinized form to rabbit cell culture lines of 'C' strain requires further support and collaboration in both Southeast and South Asia.
- Additional research is required in the following areas:
    - Basic research of immunological mechanisms to optimize subunit marker vaccines in the longer term;
    - Experimental and field studies on new subunit marker vaccines which can improve their efficacy against a broader range of genotypes;

- Assess the need for and feasibility to develop multivalent vaccines for CSF and other priority pig-specific diseases such as PRV and PRRS;
- Epidemiological research to assess the role that wild pigs and feral pigs may play in the introduction and transmission in Asia;
- Assess the performance of field based test kits for antibody and antigen detection under conventional and DIVA applications.

- Work within a One Health approach for CSF vaccine development and implementation within the context of zoonotic pig diseases that are important to the communities including influenza A H1N1, Japanese encephalitis, Streptococcus suis and cysticercosis.

Limitations

Methodology

The OIE data from South and Southeast Asia may not be entered in a standardized format and grossly underestimates the incidence and prevalence of CSFV based on recent FAO surveys of epidemiology and laboratory data quality in the region of Asia and the Pacific [52]. Based on the limited number of CSF studies supported by ILRI and AAHL the burden of disease due to CSF in Asia is significant, impacting the poorest of the poor. Although prevalence and socioeconomic studies of CSF were conducted in India and Lao PDR, there is limited published information related to CSF in Viet Nam, Indonesia, Bangladesh and Nepal. The author contacted epidemiologists in these countries to seek additional information and confirmation. ASEAN has taken a systematic approach to promote collaborative policies and research on CSF where leading countries such as Viet Nam, Philippines and Thailand play important roles and this should be considered in the subsequent phases of the LVIF project.

Gaps in knowledge or capacity impacting strategic planning and effective implementation

The key gaps and solutions that need to be addressed prior to developing a potential vaccine:

Short term:

- Assess and optimize the existing C strain tissue culture lines for wider use;
- Build vaccine production capacity for thermostable cell culture C strain vaccine based on tissue culture to increase vaccine production capacity, especially in India and Viet Nam;
- Conduct field trails with documented assessments to test the effectiveness of vaccines and diagnostic tests;
- Conduct pilot projects that include education of veterinarians, paraveterinarians and farmers on the proper use and application of vaccines and diagnostic tests.

Medium term:

- Support the development of C strain vaccines with DIVA capability with the private sector involvement for cost effective and sustainable eradication of CSF;

- Develop a cheap and effective test kit for virus detection for smallholders to meet the challenge of the predominant genotypes in Asia from the acute form (genotype 1) to the chronic form (genotype 2) which results in silent carriers.
- Conduct epidemiological research and risk assessments in Asia at the interface of commercial pig - smallholder pig production units - wild boar and feral pigs;

Long term:

- Further develop subunit marker vaccines that can eliminate all three genotypes;
- Continue basic research immunological properties of all C strain vaccines and subunit marker vaccines;
- Assess needs for oral vaccines for wild and expand the use to backyard pigs in Asia.

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